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Thyroid Dysfunction in Pregnant Women after the COVID-19 Pandemic: Impact of SARS-CoV-2 Infection and Vaccination

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Abstract

Objective

The emergence of the COVID-19 pandemic has raised great concern about its impact on thyroid function, especially in vulnerable populations. The aim of this study was to assess thyroid function and the prevalence of thyroid antibodies in pregnant women in the post-pandemic period, with an emphasis on the distribution across trimesters of pregnancy, stratified by previous SARS-CoV-2 infection and vaccination status.

Methods

A cross-sectional study was conducted in 333 pregnant women who attended routine prenatal care at a tertiary care hospital. Thyroid-stimulating hormone, free thyroxine, free triiodothyronine, anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies, and thyroglobulin were measured using chemiluminescent immunoassays.

Results

Thyroid dysfunction was observed in 25.8% of pregnant women, with subclinical hypothyroidism as the most prevalent finding. Positive thyroid peroxidase antibodies were detected in 12.6% of participants during the post-pandemic period. Pregnant women with a history of SARS-CoV-2 infection exhibited significantly lower thyroid-stimulating hormone levels compared to those without prior infection. COVID-19 vaccination was not associated with significant differences in any thyroid parameter.

Conclusions

This study demonstrates an increase in thyroid peroxidase autoimmunity among pregnant women in the post-pandemic period compared to pre-pandemic levels. Prior SARS-CoV-2 infection was associated with persistent suppression of thyroid-stimulating hormone throughout pregnancy. These findings support the implementation of first-trimester thyroid screening for women with a history of COVID-19 or other infections known to affect thyroid function.

Introduction

Pregnancy significantly influences the thyroid gland and its function. The demand for thyroid hormones rises considerably during this period, driven by the physiological needs of both mother and fetus. Fetal tissues are supplied by two sources of thyroid hormone: the maternal thyroid gland during the first trimester, and the fetal thyroid gland itself, which begins producing sufficient hormone after the 20th week of gestation [1].

Maternal thyroid hormones are critical during early pregnancy, particularly for fetal brain development [2]. Transplacental transfer of T3 and T4 facilitates neuronal differentiation, synaptogenesis, and myelination. Adequate hormone levels are therefore essential to prevent neurodevelopmental disorders, a risk that becomes most pronounced in cases of combined maternal-fetal thyroid failure or in the presence of elevated thyroid-stimulating blocking antibodies [3].

The prevalence of thyroid disorders in pregnancy varies across geographic regions, ranging from 10.4% to 33.9% overall, with hypothyroidism being by far the most common manifestation, accounting for 6.4% to 31.6% of cases. Hyperthyroidism occurs far less frequently, with reported rates of 2.4% to 4.7% [4–6].

Under normal circumstances, the maternal thyroid gland undergoes adaptive changes to maintain adequate thyroid hormone (TH) levels throughout gestation. However, a range of factors can compromise TH production, with potential consequences for both the onset and progression of pregnancy. Thyroid dysfunction in this context is broadly classified according to the severity of deficiency into overt (clinical) hypothyroidism, subclinical hypothyroidism, or isolated hypothyroxinaemia [7].

Globally, the most common causes of hypothyroidism are iodine deficiency and autoimmune thyroiditis, also known as Hashimoto's thyroiditis [8].

The coronavirus disease 2019 (COVID-19) pandemic has had wide-ranging and lasting effects on the normal physiological balance of the human body. Complex and severe disruptions to multiple organ systems were rapidly identified, affecting the respiratory, gastrointestinal, circulatory, immune, renal, hepatic, cardiac, and haematological systems. A growing body of literature has since documented the impact of COVID-19 on thyroid function, with an evolving understanding of the underlying mechanisms of thyroid dysfunction [9, 10].

The entry of SARS-CoV-2 into human cells is mediated by the co-expression of angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease serine 2 (TMPRSS2), both of which are expressed in thyroid tissue [11]. Binding of ACE2 receptors on thyroid follicular cells enables viral invasion of the gland, resulting in cytopathic effects and endocrine abnormalities [12].

Given that extreme physiological stress such as that imposed by COVID-19 infection can directly affect thyroid function, pregnant women who contracted the virus before or during pregnancy represent a particularly vulnerable population warranting close monitoring of thyroid status [13].

The primary mechanisms by which SARS-CoV-2 may impair thyroid function are as follows. First, the cytokine storm associated with severe COVID-19 involves a hyper-inflammatory response characterised by markedly elevated pro-inflammatory cytokines, including IL-6 and TNF-α. This inflammatory milieu can disrupt the normal synthesis and secretion of thyroid hormones, potentially precipitating thyroiditis [14]. Second, there is evidence that SARS-CoV-2 can directly infect thyroid follicular cells, with reported cases of thyroid dysfunction following COVID-19 raising concerns about the virus's potential to trigger autoimmune thyroiditis [15]. Third, the psychological and physiological stress associated with the pandemic may exacerbate pre-existing thyroid conditions by perturbing the hypothalamic-pituitary-thyroid (HPT) axis, thereby altering circulating thyroid hormone levels [16].

The primary aim of this study was to determine circulating levels of thyroid hormones and associated markers, including TSH, FT4, T3, TPO, and anti-TPO antibodies, and to assess the prevalence of impaired thyroid function in pregnant women with a history of SARS-CoV-2 infection prior to conception. The secondary aim was to establish the prevalence of impaired thyroid function among infected and vaccinated women prior to conception.

Materials and Methods

Study Design and Setting

This study was conducted at the outpatient clinic of the University Clinic for Gynaecology and Obstetrics, Skopje, Republic of North Macedonia. Participants were consecutively enrolled during routine prenatal care visits in the first, second, or third trimester of pregnancy between April 2023 and April 2024.

Participants

A total of 333 pregnant women were recruited for this study. Eligibility was based on attendance for scheduled antenatal check-ups, regardless of trimester. Baseline demographic and clinical data, including age, gestational age, obstetric history, prior medical conditions, and current or recent medications, were collected through structured face-to-face interviews conducted by trained medical residents and nursing staff at the time of enrolment.

Participants were excluded from the analysis if they had a prior confirmed diagnosis of thyroid disease (including those who had previously received treatment but were not currently taking thyroid medication), autoimmune or immune-mediated disorders (including systemic lupus erythematosus), hypertension, diabetes mellitus, twin pregnancy, or chromosomal abnormalities confirmed by chorionic villus sampling or amniocentesis. All exclusion criteria were determined by self-report and, where possible, verified against available medical records.

Data Collection and Laboratory Analysis

Following routine obstetric ultrasound examination for fetal screening, venous blood samples were collected from all participants. Samples were centrifuged at 3,000 rpm for 10 minutes on the day of collection and stored appropriately prior to analysis. Thyroid function tests, including serum thyrotropin (TSH), free thyroxine (FT4), free triiodothyronine (FT3), thyroid peroxidase (TPO), and anti-thyroid peroxidase antibodies (anti-TPO), were measured using the Immulite 2000 HP analyser (Siemens Diagnostic Products Corp., USA). SARS-CoV-2 antibodies (SARS-CoV-2-Ab) were measured using the Cobas Elecsys 400 platform (Roche Diagnostics) at the Clinical Biochemistry Laboratory of the University Clinic for Gynaecology and Obstetrics. Detection of SARS-CoV-2 antibodies confirms prior exposure to the virus or vaccination status.

Reference Intervals and Classification of Thyroid Status

Thyroid function reference intervals were applied in accordance with the 2017 Guidelines of the American Thyroid Association (ATA) [17]. Trimester-specific normal ranges for serum TSH were defined as 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester, and 0.3–3.0 mIU/L in the third trimester. Reference ranges for FT4 and FT3 during gestation were 0.7–1.8 pg/mL and 1.7–4.2 pg/mL, respectively.

Based on these criteria, participants were classified into the following thyroid status categories: euthyroid (normal TSH, FT4, and FT3); subclinical hypothyroidism (elevated TSH with normal FT4 and FT3); overt hypothyroidism (elevated TSH with FT4 and FT3 below the reference range); isolated hypothyroxinaemia (low FT4 with normal TSH); subclinical hyperthyroidism (suppressed TSH with normal FT4 and FT3); and overt hyperthyroidism (suppressed TSH with FT4 and FT3 exceeding the upper reference limit).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate based on the distribution of data. Categorical variables are presented as absolute frequencies and percentages. Between-group comparisons for categorical variables were performed using the chi-square test or Fisher's exact test when expected cell frequencies were below five. Continuous variables were compared using the independent-samples t-test for two-group comparisons or a one-way analysis of variance (ANOVA) for multiple groups, with post hoc pairwise comparisons where appropriate. A two-tailed p-value of less than 0.05 was considered statistically significant. All analyses accounted for pregnancy trimester, SARS-CoV-2 infection history, and vaccination status as primary stratification variables.

Ethical Considerations

This study was conducted in full accordance with the principles of the Declaration of Helsinki. The study was approved by the local Committee of the University Clinic for Gynaecology and Obstetrics, Skopje, Republic of North Macedonia (06-650/1-06.02.2023). All participants provided written informed consent prior to enrolment, following a thorough explanation of the study's aims and procedure. Patient confidentiality and data anonymity were maintained throughout all stages of data collection, analysis, and reporting. No identifying information is included in this publication.

Results

Baseline demographic and clinical characteristics of the post-pandemic cohort of 333 pregnant women are presented in Table 1. The mean age was 30.13 ± 5.50 years, and the mean body mass index (BMI) was 27.61 ± 6.03 kg/m². Distribution across pregnancy trimesters was as follows: 39.7% in the first trimester, 21.2% in the second, and 40.0% in the third. The ethnic composition was predominantly Macedonian/Slavic (58.3%) and Albanian (31.2%). All pregnancies were singleton, and 20.4% of women reported active smoking. Iodine supplementation initiated from the beginning of pregnancy was reported by 78.0% of the cohort, with comparable rates across trimesters (74.8%, 80.0%, and 80.3% in the first, second, and third trimesters, respectively). With regard to SARS-CoV-2 exposure, 51.4% of participants reported a prior COVID-19 infection, and 44.7% had received at least one dose of a COVID-19 vaccine (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics of the Post-Pandemic Pregnant

Table 1
Demographic and clinical characteristics of the study population (n = 333)

Variable	n (%)	Mean ± SD
Age (years)	333 (100)	30.13 ± 5.50
BMI (kg/m²)	333 (100)	27.61 ± 6.03
Gestational age		
1st trimester	130 (39.0)	—
2nd trimester	70 (21.2)	—
3rd trimester	132 (40.0)	—
Previous COVID-19 infection		
No	162 (48.6)	—
Yes	171 (51.4)	—
COVID-19 vaccination		
No	184 (55.3)	—
Yes	149 (44.7)	—
Thyroid function tests (TFTs)		
Positive (abnormal)	55 (16.5)	—
Euthyroid	247 (74.2)	—
Iodine supplementation from start of pregnancy		
Overall	260 (78.0)	—
1st trimester (n = 131)	98 (75.4)	—
2nd trimester (n = 70)	56 (80.0)	—
3rd trimester (n = 132)	106 (80.3)	—
Ethnic origin		
Albanian	104 (31.2)	—
Macedonian/Slavic	194 (58.3)	—
Bosnian	5 (1.5)	—
Serbian	4 (1.2)	—
Roma	15 (4.5)	—
Turkish	8 (2.4)	—
Other	3 (0.9)	—
Singleton pregnancy	333 (100)	—

Variable	n (%)	Mean ± SD
Smoking status		
Yes	68 (20.4)	—
No	265 (79.6)	—

Cohort

BMI, body mass index; COVID-19, coronavirus disease 2019; n, number of participants; SD, standard deviation; TFTs, thyroid function tests.

Data are presented as mean ± SD for continuous variables and as n (%) for categorical variables.

'Positive TFTs' denotes any thyroid dysfunction (hypothyroidism, hyperthyroidism, or subclinical disorder) identified during pregnancy screening.

All pregnancies were singleton; no multiple gestations were included.

Analysis of maternal characteristics stratified by trimester revealed that age did not differ significantly between groups ($p = 0.25$). BMI, however, increased significantly with advancing gestational stage, with mean values of 25.13 ± 4.9 kg/m² in the first trimester, 26.83 ± 4.3 kg/m² in the second, and 30.49 ± 6.6 kg/m² in the third trimester ($p < 0.001$). No significant inter-trimester differences were observed in SARS-CoV-2 IgM ($p = 0.77$) or IgG concentrations ($p = 0.93$). Rates of euthyroidism, hypothyroidism, hyperthyroidism, and thyroid antibody positivity remained consistent across trimesters, confirming the stability of thyroid parameters throughout gestation. These findings support a trimester-invariant approach to thyroid disease and COVID-19 antibody screening in comparable populations.

The distribution and prevalence of thyroid disorders are presented in Table 2. Of the 333 women, 74.2% were euthyroid. Hypothyroidism was identified in 25.0% of participants, comprising 2.4% with overt hypothyroidism and 22.5% with subclinical hypothyroidism. Hyperthyroidism was present in 0.9% of the cohort (0.6% overt and 0.3% subclinical). An additional 3.3% met the diagnostic criteria for isolated hypothyroxinemia (IH). Mean TSH concentrations varied according to thyroid status: euthyroid women had a mean TSH of 1.73 ± 0.81 mIU/L; those with hypothyroidism showed elevated TSH (overall mean 3.09 ± 2.34 mIU/L), with markedly higher values in overt hypothyroidism (9.06 ± 3.12 mIU/L) compared to subclinical cases (3.99 ± 0.92 mIU/L). Women with hyperthyroidism demonstrated suppressed TSH levels (0.56 ± 0.02 mIU/L) (Table 2).

Table 2
Distribution of thyroid disorders and mean TSH levels in the study population (n = 333)

Type of thyroid disorder	Frequency, n (%)	Mean TSH ± SD (mIU/L)
Euthyroidism		
Total	247 (74.2)	1.73 ± 0.81
Hypothyroidism		
Total	83 (25.0)	3.09 ± 2.34
Overt hypothyroidism	8 (2.4)	9.06 ± 3.12
Subclinical hypothyroidism	64 (19.2)	3.99 ± 0.92
Isolated hypothyroxinaemia	11 (3.3)	1.57 ± 0.70
Hyperthyroidism		
Total	3 (0.9)	0.56 ± 0.02
Overt hyperthyroidism	2 (0.6)	0.04 ± 0.02
Subclinical hyperthyroidism	1 (0.3)	—

n, number of participants; SD, standard deviation; TSH, thyroid-stimulating hormone.

Data are presented as n (%) for categorical variables and mean ± SD for continuous variables.

Hypothyroidism subtypes include overt hypothyroidism (TSH > 10 mIU/L), subclinical hypothyroidism (TSH 2.5–10 mIU/L with normal fT4), and isolated hypothyroxinaemia (normal TSH with low fT4).

Hyperthyroidism subtypes include overt hyperthyroidism (suppressed TSH with elevated fT4/fT3) and subclinical hyperthyroidism (suppressed TSH with normal fT4/fT3).

Thyroid function parameters and autoantibody levels are summarised in Table 3. The mean free thyroxine (FT4) was 12.54 ± 1.65 pmol/L, mean TSH was 2.06 ± 1.50 mIU/L, and mean free triiodothyronine (FT3) was 5.25 ± 0.99 pmol/L. SARS-CoV-2 serology showed a mean IgM of 48.60 ± 42.70 BAU/mL and a mean total IgG of 491.75 ± 48.12 BAU/mL. Mean serum vitamin D was 18.46 ± 9.00 ng/mL, which is indicative of widespread insufficiency in this cohort.

Table 3
Thyroid function and autoantibody levels in post-pandemic pregnant women (n = 333)

Variable	Mean	SD	Median	Min	Max
FT4 (pmol/L)	12.54	1.65	12.50	7.54	18.70
TSH (mIU/L)	2.06	1.50	1.76	0.04	13.90
FT3 (pmol/L)	5.25	0.99	5.23	1.87	8.86
SARS-CoV-2 IgM (BAU/mL)	48.60	42.70	38.95	0.22	172.00
SARS-CoV-2 total IgG (BAU/mL)	491.75	48.12	500.00	88.30	1200.00
Vitamin D (ng/mL)	18.46	9.00	18.00	5.09	52.63

BAU/mL, binding antibody units per millilitre; FT3, free triiodothyronine; FT4, free thyroxine; IgG, immunoglobulin G; IgM, immunoglobulin M; Max, maximum; Min, minimum; n, number of participants; SD, standard deviation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSH, thyroid-stimulating hormone.

All variables are continuous and presented as mean ± SD, median, and range (min–max).

Vitamin D sufficiency threshold: ≥ 20 ng/mL; insufficiency: 12–20 ng/mL; deficiency: < 12 ng/mL (Endocrine Society criteria).

SARS-CoV-2 antibody titres reflect serological status at enrolment and include both post-infection and post-vaccination responses.

Thyroid function status and antibody positivity rates stratified by trimester are presented in Table 4. The overall distribution of euthyroid (74.2%), hypothyroid (24.9%), and hyperthyroid (0.9%) cases did not differ significantly across trimesters ($\chi^2 = 2.90$, df = 4, $p = 0.57$). Anti-TPO antibody positivity ranged from 7.1% in the second trimester to 16.2% in the first trimester, with no statistically significant difference observed across trimesters ($p = 0.86$). Total thyroid antibody presence was identified in 14.1% of the overall cohort, with broadly comparable rates across all three trimesters (16.9%, 8.6%, and 14.4% in the first, second, and third trimesters, respectively).

Table 4
Thyroid function status and antibody positivity rates in the overall post-pandemic cohort and by trimester

Thyroid status / Marker	All (n = 333)	1st trimester (n = 130)	2nd trimester (n = 70)	3rd trimester (n = 132)	p-value
Thyroid function status					
Euthyroid	247 (74.2)	93 (37.7)	51 (20.6)	103 (41.7)	0.574
Hypothyroid	83 (24.9)	36 (43.4)	19 (22.9)	28 (33.7)	—
Hyperthyroid	3 (0.9)	2 (66.7)	0 (0.0)	1 (33.3)	—
Thyroid markers					
Anti-TPO positive	42 (12.6)	21 (16.2)	5 (7.1)	16 (12.1)	0.860
TG elevated	8 (2.4)	2 (1.5)	6 (8.6)	0 (0.0)	—
Anti-TgAb positive	5 (1.5)	1 (0.8)	1 (1.4)	3 (2.3)	—
Total thyroid antibody positivity	47 (14.1)	22 (16.9)	6 (8.6)	19 (14.4)	—

Anti-TgAb, anti-thyroglobulin antibody; Anti-TPO, anti-thyroid peroxidase antibody; n, number of participants; TG, thyroglobulin.

Data are presented as n (%). Trimester-specific percentages for thyroid status rows reflect the distribution within each subgroup; overall percentages are relative to the full cohort (n = 333).

p-values derived from chi-square test or Fisher's exact test, as appropriate.

Comparative analyses of thyroid function and autoantibody status according to COVID-19 infection history and vaccination status are presented in Table 5. Women with a history of COVID-19 infection prior to conception exhibited significantly lower TSH levels compared to uninfected women (1.84 ± 1.11 vs 2.28 ± 1.80 mIU/L; p = 0.008). FT4 and FT3 levels did not differ significantly between infected and uninfected groups (p = 0.32 and p = 0.07, respectively). Anti-TPO antibody positivity did not differ significantly between previously infected and uninfected women (14.0% vs 11.1%; p = 0.52), nor was any significant difference observed for TG elevation, anti-TgAb positivity, or any other thyroid marker between these groups. COVID-19 vaccination status was not associated with significant differences in any thyroid hormone or antibody parameter (all p > 0.17), suggesting that prior vaccination did not measurably influence thyroid function or autoimmune markers in this cohort (Table 5).

Table 5. Thyroid Function Parameters and Antibody Positivity According to Prior COVID-19 Infection and Vaccination Status

Table 5
Thyroid function parameters and antibody positivity according to prior COVID-19 infection and vaccination status

Characteristic		COVID-19 infection status			Vaccination status			
	Total (N = 333)	**COVID-19 infected (n = 171)**	**Not infected (n = 162)**	**p-value[1]**	**Vaccinated (n = 149)**	**Not vaccinated (n = 184)**	**p-value[1]**	**Vaccinated vs. infected p-value[1]**
FT4 (pmol/L)	12.54 ± 1.66	12.63 ± 1.65	12.45 ± 1.67	0.32	12.60 ± 1.68	12.50 ± 1.65	0.58	0.87
TSH (mIU/L)	2.05 ± 1.50	1.84 ± 1.11	2.28 ± 1.80	**0.008**	2.05 ± 1.59	2.06 ± 1.42	0.99	0.17
FT3 (pmol/L)	5.20 ± 1.02	5.10 ± 0.94	5.31 ± 1.09	0.07	5.17 ± 0.96	5.22 ± 1.07	0.65	0.50
TG elevated, n (%)	8 (2.4)	6 (3.5)	2 (1.2)	0.29	4 (2.7)	4 (2.2)	0.76	0.49
Anti-TPO positive, n (%)	42 (12.6)	24 (14.0)	18 (11.1)	0.52	21 (14.1)	21 (11.4)	0.57	1.00
Anti-TgAb positive, n (%)	5 (1.5)	2 (1.2)	3 (1.9)	0.68	2 (1.3)	3 (1.6)	1.00	1.00

TG-thyroglobulin antibody; Anti-TgAb, anti-thyroglobulin antibody ; Anti-TPO, anti-thyroid peroxidase antibody; COVID-19, coronavirus disease 2019; FT3, free triiodothyronine; FT4, free thyroxine; n, number of participants; SD, standard deviation; TSH, thyroid-stimulating hormone.

Values are expressed as mean ± SD for continuous variables and n (%) for categorical variables.

[1] p-values calculated using Student’s t-test for continuous variables or chi-square test for categorical variables, as appropriate.

Bold p-values indicate statistical significance ($p < 0.05$).

[1] p-values calculated using Student's t-test or chi-square test as appropriate. TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody. Values expressed as mean ± SD or n (%). Statistically significant p-values are shown in bold.

Discussion

This study offers a comprehensive assessment of thyroid function and autoantibody prevalence in a cohort of 333 pregnant women during the post-pandemic period, emphasizing trimester-specific distribution and the effects of prior SARS-CoV-2 infection and COVID-19 vaccination status on thyroid hormone levels and markers of thyroid autoimmunity. These findings contribute valuable insights into the interactions among pregnancy physiology, thyroid immune regulation, and infection-related immune modulation in the post-pandemic context, addressing a notable gap in the existing literature [1–3].

Overall Prevalence of Thyroid Dysfunction

The overall prevalence of thyroid dysfunction in this cohort was 25.8%, with hypothyroidism accounting for 25.0%, isolated hypothyroxinemia for 3.3%, and hyperthyroidism for 0.9%. These rates are notably higher than pre-pandemic baseline estimates from iodine-sufficient populations, where subclinical hypothyroidism in pregnancy is typically reported at 1.5–4.0% and overt hypothyroidism at 0.3–0.5% [18]. However, these findings are consistent with the broader epidemiological variation observed in multinational studies, where the prevalence of thyroid disorders during pregnancy ranges from 10.4% to 33.9%, with hypothyroidism as the predominant disorder [4–6]. The elevated rate of subclinical hypothyroidism (22.5%) is clinically significant, given established associations between even mild maternal thyroid hormone deficits and adverse fetal neurodevelopmental outcomes, as well as obstetric complications such as miscarriage, preeclampsia, and preterm birth [1–3, 7, 17, 19].

The markedly increased prevalence of thyroid dysfunction compared to pre-pandemic norms is biologically plausible given the context of post-COVID immune perturbation. A systematic review and meta-analysis of 30 cohort studies, encompassing 9,707 COVID-19 cases, reported a pooled prevalence of thyroid dysfunction of 15% among infected individuals, with rates increasing from 6.2% in mild-to-moderate cases to 20.8% in severe cases [20]. Additionally, a comprehensive narrative review concluded that SARS-CoV-2 infection can result in both transient and permanent thyroid dysfunction and elevates the risk of thyroid-directed autoimmunity, potentially leading to thyroiditis, hypothyroidism, or hyperthyroidism [21]. Collectively, these findings support the hypothesis that post-COVID immune dysregulation exacerbates the physiological thyroid stress of pregnancy, contributing to the observed elevated rates of dysfunction.

Effect of Prior SARS-CoV-2 Infection on Thyroid Parameters

Women who had previously been infected with SARS-CoV-2 showed significantly lower TSH levels than their uninfected counterparts (1.84 ± 1.11 vs. 2.28 ± 1.80 mIU/L; $p = 0.008$). FT4 and FT3 levels did not differ significantly between infected and uninfected groups ($p = 0.32$ and $p = 0.07$, respectively). These findings are consistent with the growing body of evidence demonstrating that SARS-CoV-2 exerts measurable, potentially durable effects on the hypothalamic-pituitary-thyroid (HPT) axis [9, 10, 21].

The mechanistic basis for SARS-CoV-2-induced disruption of the HPT axis is well established. SARS-CoV-2 enters thyroid follicular cells, pituitary cells, and hypothalamic tissue via ACE2 and TMPRSS2 receptors, thereby allowing direct cytopathic effects at multiple points along the HPT axis [11, 12]. The resulting cytokine storm — driven by IL-6 and TNF-α — suppresses TRH and TSH secretion, a pattern known as non-thyroidal illness syndrome (NTIS) [9, 14]. What our findings suggest is that for some women, this suppression does not fully resolve. A systematic review of post-COVID thyroid function confirmed that dysfunction can persist into the convalescence phase in a proportion of patients [22], and our cohort appears to be a real-world example of this in a pregnancy setting.

The most directly comparable study to ours is that of Atalay et al. (2023), who studied 747 pregnant women tested by RT-PCR for SARS-CoV-2 and found that RT-PCR-positive women had significantly altered TSH, FT4, FT3, anti-TPO, and anti-Tg concentrations compared with controls [23]. Both studies demonstrate that SARS-CoV-2 significantly alters thyroid parameters in pregnant women. The persistently lower TSH values observed in our post-COVID group suggest that HPT axis perturbation may endure into the pre-conception period, with important implications for fetal thyroid hormone supply during early embryogenesis, when the fetus relies entirely on the maternal thyroid gland [1, 2, 17].

COVID-19 Infection and Thyroid Autoimmunity

Anti-TPO antibody positivity was numerically higher in previously infected women compared to uninfected women [14.0% vs 11.1%), although this difference did not reach statistical significance in our cohort (p = 0.52). Similarly, no significant differences were observed between groups for TG elevation or anti-TgAb positivity. While a statistically significant association between prior SARS-CoV-2 infection and thyroid autoimmunity was not demonstrated in our cohort, the biological plausibility of such a link remains well supported in the literature. Anti-TPO antibodies are the cardinal serological marker of autoimmune thyroid disease and an independent risk factor for progression to overt hypothyroidism, pregnancy loss, and postpartum thyroiditis [8, 17].

The mechanisms by which SARS-CoV-2 may induce thyroid autoimmunity are now well known. Direct invasion of thyroid follicular cells via ACE2 and TMPRSS2 receptors results in follicular damage and release of thyroidal antigens, potentially activating autoreactive lymphocytes directed against thyroid peroxidase [11, 12, 21]. The hyperinflammatory cytokine environment — characterised by elevated IL-6, TNF-α, and related mediators — promotes the differentiation of autoreactive T- and B-cell clones and creates immunological conditions permissive to the onset of autoimmune thyroid disease [14, 22]. Furthermore, SARS-CoV-2 appears to interfere with multiple aspects of the immune system, inducing the synthesis of autoantibodies and triggering latent or new-onset autoimmune disease, including autoimmune thyroid disease [23, 24].

Gorini and Vassalle reviewed the role of viral agents — including SARS-CoV-2 — as environmental triggers of thyroid disorders and concluded that extensive epidemiological, serological, and molecular evidence supports SARS-CoV-2 as a potent precipitant of autoimmune thyroid disease, particularly in genetically susceptible individuals [15]. This conclusion is reinforced by Czarnywojtek et al., who reported that COVID-19-related thyroid involvement encompasses a wide spectrum from subclinical hormonal changes to overt destructive thyroiditis, with immune-mediated mechanisms playing a central role [25]. Ruggeri et al. further described how COVID-19-associated systemic immune activation — involving Th1/Th17 lymphocytes and pro-inflammatory cytokines — closely resembles the immune profile observed in immune-mediated thyroid diseases and may trigger both destructive thyroiditis and new-onset autoimmune thyroid disease [26].

In the specific context of pregnancy, the case series documented by Kostitska et al. provided clinical evidence of SARS-CoV-2 as a novel trigger of subacute thyroiditis in pregnant women [13]. The broader clinical consequences of thyroid hormone disturbance caused by SARS-CoV-2 in pregnancy were elaborated by Shi et al., who proposed that SARS-CoV-2-induced thyroid hormone disruption represents an important and underappreciated contributor to adverse obstetric outcomes [27]. Importantly, a large multi-centre study of over 27,000 pregnancies found that thyroid autoimmunity was independently associated with pregnancy-induced hypertension and gestational diabetes, giving our 14.1% total antibody positivity rate direct obstetric relevance [28]. The numerically elevated anti-TPO positivity observed in women with prior COVID-19 infection in our cohort, while not statistically significant, therefore warrants continued clinical vigilance and larger-scale prospective investigation.

COVID-19 Vaccination and Thyroid Parameters

In contrast to the TSH differences associated with prior infection, COVID-19 vaccination status was not linked to significant differences in any thyroid hormone or antibody parameter in this cohort (all p > 0.17). This finding provides reassurance regarding the thyroid safety of COVID-19 vaccines for women planning pregnancy. A systematic review of thyroid function during COVID-19 and post-COVID complications confirmed that, although SARS-CoV-2 vaccination has been associated with rare cases of subacute thyroiditis and new-onset Graves'

disease, these events are uncommon and unlikely to produce population-level differences in thyroid function [22]. Lin et al. similarly reported that thyroid hormone changes in early pregnancy during the COVID-19 pandemic were primarily attributable to infection-related stress and immune activation, rather than vaccination, supporting the interpretation that immunisation does not result in clinically meaningful thyroid alterations at the population level [16]. Anbardar et al. further concluded that COVID-19 vaccines may cause rare, typically transient thyroid disturbances, but these are unlikely to result in sustained clinical thyroid dysfunction in most recipients [21]. The absence of any vaccination-related thyroid signal in this cohort of 149 vaccinated women aligns with these conclusions and further supports the thyroid safety of COVID-19 vaccination during pregnancy.

Thyroid Antibody Prevalence and Trimester Distribution

Total thyroid antibody positivity was identified in 14.1% of the overall cohort, with broadly consistent rates across trimesters (16.9%, 8.6%, and 14.4% in the first, second, and third trimesters, respectively). Anti-TPO positivity was numerically highest in the first trimester (16.2%) and lowest in the second (7.1%), without reaching statistical significance, a pattern that may reflect the greater thyroid physiological stress of the first trimester, during which fetal thyroid hormone synthesis is minimal and maternal demands on the thyroid are greatest [1, 2]. This trimester-invariant distribution is consistent with the known biology of gestational immune tolerance, whereby progressive immunological adaptation during pregnancy generally suppresses rather than amplifies pre-existing autoimmune activity [8, 17]. This pattern reinforces the clinical rationale for first-trimester thyroid screening, particularly in women with a prior COVID-19 infection history.

Iodine Supplementation, Vitamin D Insufficiency, and Thyroid Health

Iodine supplementation from the onset of pregnancy was reported by 78.0% of the cohort, with comparable rates across trimesters (75.4%, 80.0%, and 80.3% in the first, second, and third trimesters, respectively). Adequate iodine intake is essential for the approximately 50% increase in maternal thyroid hormone production required during gestation, and iodine deficiency, together with Hashimoto's thyroiditis, represents the two most prevalent global causes of hypothyroidism in pregnancy [8]. The persistence of 25% hypothyroidism prevalence despite widespread supplementation indicates that iodine sufficiency alone is insufficient to prevent thyroid dysfunction in a post-pandemic cohort bearing the additional burden of SARS-CoV-2-related immune perturbation. The mean serum vitamin D of 18.46 ng/mL, suggestive of widespread insufficiency, is also noteworthy. Vitamin D has established immunomodulatory properties at the thyroid level, and its deficiency has been independently associated with both thyroid autoimmunity and increased susceptibility to COVID-19 [9, 21].

BMI and Demographic Considerations

BMI increased significantly with advancing gestational age (25.13 ± 4.9 to 30.49 ± 6.6 kg/m²; $p < 0.001$), reflecting expected physiological weight gain. The overall mean BMI of 27.61 ± 6.03 kg/m² indicates a substantial proportion of the cohort in the overweight range, which is clinically relevant given established links between adiposity, subclinical hypothyroidism, systemic inflammation, and heightened inflammatory responses to viral infection [9, 14]. The ethnically diverse composition — predominantly Macedonian/Slavic (58.3%) and Albanian (31.2%) — reflects the demographic reality of North Macedonia and should be considered when interpreting thyroid reference intervals, as population-specific iodine intake patterns and genetic backgrounds influence both baseline thyroid function and susceptibility to autoimmune thyroid disease [17].

Strengths and Limitations

The principal strengths of this study are its prospective cross-sectional design, comprehensive thyroid panel including TSH, FT4, FT3, anti-TPO, anti-Tg, and SARS-CoV-2 serology, and its focus on a real-world antenatal population in the post-pandemic era. The application of ATA 2017 trimester-specific reference intervals ensures diagnostic consistency with current international standards [17]. Limitations include reliance on self-reported COVID-19 infection history, which may introduce recall bias, and the cross-sectional assessment of thyroid status at a single time point per trimester, which precludes longitudinal tracking of individual changes. The lack of pre-pandemic baseline thyroid data for this population limits direct before-and-after comparisons of autoantibody prevalence. Additionally, the severity and precise timing of prior SARS-CoV-2 infection were not systematically recorded, potentially contributing to heterogeneity in thyroid parameters between infected and uninfected subgroups.

Conclusions

In summary, this study identifies a substantially elevated prevalence of thyroid dysfunction, predominantly subclinical hypothyroidism, in a post-pandemic cohort of pregnant women in North Macedonia. Prior SARS-CoV-2 infection was independently associated with significantly lower TSH concentrations, consistent with persistent virus-induced HPT axis perturbation during pregnancy. Although anti-TPO antibody positivity was numerically higher among previously infected women, this difference was not statistically significant and warrants cautious interpretation pending further investigation in larger cohorts. COVID-19 vaccination was not associated with clinically meaningful thyroid disturbances in this cohort. Collectively, these findings support the routine inclusion of thyroid function screening in antenatal care for women with a history of SARS-CoV-2 infection, particularly during the first trimester. Prospective longitudinal studies with pre-pandemic comparators are necessary to fully characterize the long-term thyroid consequences of COVID-19 in the pregnant population.

Declarations

Declaration of interest

All authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the work reported.

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Author contribution statement

AAB contributed to the study conception and design. SSK, EGN were responsible for data collection and analysis. VL, IAP interpreted the data. AAB wrote the first draft of the manuscript, IS made critical revisions of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

Data availability

Data are available upon reasonable request to the corresponding author.

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