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LETTER

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Mild and asymptomatic SARS-CoV-2 infection is not associated with progression of thyroid dysfunction or thyroid autoimmunity

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Dear Editor,

The novel coronavirus (SARS-CoV-2) pandemic has emerged as a major public health challenge, affecting more than 380 million people globally and causing more than 5.6 million deaths.[1] It is well understood that coronavirus disease (COVID-19) manifestations can extend beyond the respiratory system and involve several endocrine organs, including the thyroid gland. A variety of thyroid abnormalities have been reported with SARS-CoV-2 infection, both during the acute and post-acute phases. These include reversible non-thyroidal illness syndrome and thyrotoxicosis related to destructive thyroiditis during the acute phase, and cases of subacute thyroiditis and new-onset or recurrent Graves' disease after recovery from viral infection.[2,3] The proposed mechanisms include: (a) direct damage through virus entry into thyroid follicular cells via angiotensin-converting enzyme 2 receptor and (b) indirect damage in terms of development or progression of thyroid autoimmunity through the immunological trigger induced by the pro-inflammatory state of infection, molecular mimicry, and infection-related stress. However, there are certain limitations to the available data: (a) majority of information is derived from individual case reports or small case series, (b) where large size studies are available, they involved hospitalised patients who suffer from more severe disease than in the community and (c) most studies do not report pre-COVID thyroid function results, making causality assessment difficult.

Against this backdrop, we performed a longitudinal study that involved an established research cohort sampled at two time points: pre-COVID (2016–2019) and peri-COVID period (August 2020 to February 2021). This cohort comprised of women with history of hyperglycaemia or normoglycaemia in pregnancy who were followed up in the post-partum period along with their spouses. The median (interquartile range) interval since the index delivery at the first study visit was 13.5 (7.3, 37.3) months. At both visits, a study questionnaire was completed and blood was collected for measurement of total T4 (*N*: 65.6–181.5 nmol/L), thyrotropin (TSH; *N*: 0.27–4.2 mIU/L) and thyroid peroxidase (TPO; positive: >34 IU/mL) antibody. These analytes were measured using competitive binding (T4 and TPO) or sandwich (TSH) electrochemiluminescence immunoassay (Roche Diagnostics). At the second visit, participants were also tested for SARS-CoV-2 S1/S2 IgG antibody (positive: ≥15 AU/ml) using an indirect chemiluminescence immunoassay (DiaSorin S.p.A.). Since the last study sample was collected before the onset of national vaccination programme, SARS-CoV-2 seropositivity was considered as a surrogate for infection.

Participants with seropositive status but no history of documented viral infection were considered to have mild/asymptomatic infection. Other study definitions included: (a) euthyroidism, if both T4 and TSH were normal, (b) subclinical hypothyroidism, if T4 was normal, but TSH was mildly elevated to less than 10 mIU/L (4.21–9.99 mIU/L) and (c) overt hypothyroidism, if TSH was more than 10 mIU/L, regardless of T4 levels or already on levothyroxine supplementation. We used a cut-off level of 10 mIU/L for distinction between two forms of hypothyroidism because: (a) nearly 90% of patients with subclinical hypothyroidism have TSH elevation lower than this cut-off and (b) most authorities suggest a need for levothyroxine treatment beyond this threshold, which we interpreted as overt hypothyroidism in the context of this study. We included participants with euthyroidism and subclinical hypothyroidism at baseline, and defined progression of thyroid dysfunction as change from euthyroidism to subclinical or overt hypothyroidism, and from subclinical to overt hypothyroidism. Similarly, a change from a negative to positive TPO status was defined as new-onset thyroid autoimmunity. We excluded participants with secondary hypothyroidism, overt hypothyroidism or thyrotoxicosis at the baseline evaluation. Statistical methods have been provided in Appendix S1.

The study protocol was approved by the institutional ethics committee.

The baseline characteristics of study participants ($n = 240$, 50% females) have been summarized in Table 1. The mean age and body mass index were 35.2 ± 5.4 years and 25.6 ± 3.9 kg/m^2, respectively. One hundred and ninety-three (81.1%) participants were euthyroid, while rest 45 (18.9%) had subclinical hypothyroidism. Twenty (8.5%) participants tested TPO antibody positive with median antibody levels of 108.2 (73.2, 191.6) IU/ml. The mean duration between the two study visits was 20.2 ± 5.1 months. A total of 109 participants (45.4%) were seropositive for SARS-CoV-2 IgG (infection group), median antibody levels being 56.9 (33.9, 93.7) AU/ml. Of these seropositive participants, only 27 had a history of documented infection (reverse transcription polymerase chain reaction or rapid antigen test), implying that rest 82 (75.2%) had mild/asymptomatic infection. Data on follow-up thyroid function were available in 222 (93.2%) participants. Progression of thyroid dysfunction occurred in 22 (9.9%) participants (euthyroidism to subclinical hypothyroidism: $n = 16$, subclinical hypothyroidism to overt hypothyroidism: $n = 4$ and euthyroidism to overt hypothyroidism: $n = 2$). However, there was no significant difference in proportion of participants who progressed in the infected (12/100, 12%) and non-infected groups (10/122, 8.2%; $p = .345$). The unadjusted odds ratio (OR) for association between viral infection and thyroid category progression was 1.53 (95% confidence interval [CI], 0.63, 3.7; $p = .348$). After adjustment for age, gender, duration between two visits, baseline body mass index (BMI) and change in BMI, adjusted OR was 1.50 (95% CI, 0.62, 3.67; $p = .369$). TPO category progression events were small in number ($n = 4$, 1.7%); the difference between infected and noninfected groups for this outcome was not significant (2.8% vs. 0.8%; $p = .335$).

We measured thyroid function parameters before and during the course of COVID-19 pandemic, and found that predominant mild and asymptomatic SARS-CoV-2 infection was not associated with thyroid dysfunction or new-onset thyroid autoimmunity. Previously, Clarke et al.[4] reported normal thyroid function among 68 patients without pre-existing thyroid dysfunction evaluated at ≥3 months following the index infection (moderate, severe or critical disease in 83% of study participants). The authors concluded that thyroid function is preserved in COVID survivors and the symptoms of fatigue commonly reported in the post-acute phase are not explained by thyroid dysfunction. Our findings are similar to those reported by Clarke et al.[4]; however, our study involved participants with predominant mild and asymptomatic infection, a disease pattern more representative of that seen in the community. Our study has some limitations. The baseline prevalence of subclinical hypothyroidism was relatively high for a young study population. This may reflect a selection bias related to a higher referral of pregnant women with co-existing thyroid dysfunction to our department, who were eventually enroled in this post-partum cohort. Rapid decay of antibody titre has been reported following mild SARS-CoV-2 infection.[5] We could have potentially misclassified such cases under the non-infected group. The study events were relatively small in number and participants were evaluated at a short duration (<1 year) following the index infection (first case of COVID-19 in this part of country was reported in March 2020 and the last follow-up visit occurred in February 2021). Thus, the findings of our study should be interpreted in light of these limitations.

TABLE 1 Baseline characteristics of study participants ($n = 240$)

Female	120 (50%)
Age (years)	35.2 ± 5.4
Occupation, employed	141 (58.8%)
Education, graduate or above	151 (62.9%)
Body mass index (kg/m^2)	25.6 ± 3.9
T4 (nmol/L)[a]	106.8 ± 20.6
TSH (mIU/L)[a]	3.1 ± 1.5
TPO (IU/ml)[b]	12.7 (9.7, 17.5)
Thyroid status[a]	
Euthyroidism	193 (81.1%)
Subclinical hypothyroidism	45 (18.9%)
TPO positivity[b]	20 (8.5%)

[a] $n = 238$.
[b] $n = 235$.

To conclude, in this longitudinal cohort study, participants evaluated at a short duration (<1 year) following predominant mild and asymptomatic SARS-CoV-2 infection did not manifest with progression of thyroid dysfunction or thyroid autoimmunity. Data from large multicenter registries that provide long-term trajectories of thyroid function in the context of SARS-CoV-2 infection are needed in the near future.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

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