

# **Answer to 1<sup>st</sup> review**

Reviewer Name: Anonymous

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Specific Comments To Authors: I read this manuscript with interest. The authors report a pregnant woman with COVID-19 and seizures classified as a thyroid storm complicating Graves' disease in the presence of papillary thyroid carcinoma. They concluded that the thyroid storm was related to SARS-CoV-2 infection in this pregnant woman and that such a relationship has not been reported before. The manuscript is well written, although some mistakes should be addressed in the English grammar and spelling. I would like to make some suggestions to improve the manuscript: -

They should report the epidemiological data of thyroid storms in pregnant women beyond COVID-19.

- ✓ We have added this information.
- ✓ Hyperthyroidism can develop in about 0.2% of pregnant women, and Graves' disease is responsible for almost 95% of the cases of hyperthyroidism during pregnancy. A TS is a rare condition that affects about 1% of pregnant women with hyperthyroidism (Discussion)

The type of tests for COVID-19 should be reported.

- ✓ We have corrected this.
- ✓ Nasopharyngeal COVID-19 polymerase chain reaction (PCR) test

It is important to use the WHO grading system for the severity of COVID-19 in this patient.

- ✓ We have added this information.
- ✓ According to the World Health Organization (WHO) COVID-19 Ordinal Scale for

clinical improvement, this was a severe disease state that required hospitalization for a score of 6 (Table 1) [5]. (Case presentation - History of present illness)

Why was fever considered only related to thyroid storm and not to COVID-19?

- ✓ We have clarified this in the manuscript.
- ✓ In the case of our patient, the fever may have been caused by not only COVID-19 but also by the TS induced by COVID-19. (Discussion – Symptoms)

It is not clear whether the patient had presented with status epilepticus or episodic seizures.

- ✓ We have clarified this.
- ✓ Our patient had a generalized tonic-clonic type of seizure, status epilepticus (SE). Specifically, recurrent seizures occurred despite the use of appropriate doses of midazolam, and these were classified as refractory SE (RSE). (Discussion – Symptoms)

Can it be classified as new-onset refractory status (NORSE)? Febrile infection-related epilepsy syndrome (FIRES)?

- ✓ We have clarified these concerns.
- ✓ In the present case, the RSE was classified as new-onset RSE (NORSE) because there were no previous neurological diseases and no preexisting toxic and metabolic causes [28]. In the case of our patient, the fever may have been caused by not only COVID-19 but also by the TS induced by COVID-19. Thus, if SE is caused by the fever of COVID-19, it can also be classified as febrile infection-related epilepsy syndrome (FIRES), which is a subset of NORSE [28]. (Discussion – Symptoms)

I believe that the authors' first impression was "seizures and altered consciousness due to eclampsia". -Were cerebral venous sinus thrombosis and meningoencephalitis adequately addressed? Why is it not a posterior reversible encephalopathy syndrome (PRES)? -The authors

should also discuss the possibility of a paraneoplastic neurological syndrome in the presence of thyroid cancer.

- ✓ We have added brief discussions on these conditions.
- ✓ There are several neurological diseases that must be differentiated from the perspective of accompanying SE with the help of neurologists. In consideration of the patient's condition, neurological examinations and brain imaging studies should be performed to differentiate intracranial diseases. Among these, the differential diagnoses for cerebral venous sinus thrombosis, meningoencephalitis, and posterior reversible encephalopathy syndrome should be included. (Discussion – Diagnosis)
- ✓ Paraneoplastic neurologic syndrome (PNS) also needs to be differentially diagnosed as an additional disease. PNS is an autoimmune disease and may present with several clinical manifestations, such as encephalitis, autonomic dysfunction, peripheral neuropathy, cerebellar ataxia, and visual disturbances [33]. Clinicians should be hence alert to the possibility of PNS if the patient has a past or family history of cancer or autoimmune disease [33]. (Discussion – Diagnosis)

Was the final diagnostic "seizures" or status epilepticus?

- ✓ The seizures persisted even after endotracheal intubation, and recurrent seizures occurred without recovery of consciousness, which indicated status epilepticus. (Physical examination)

In the Discussion section, I would like to suggest that the authors report similarities and differences with other cases of thyroid storm related to COVID-19 beyond pregnancy. Also, they should discuss how pregnancy can trigger thyroid storms in the Etiology subsection.

- ✓ We have added these details.
- ✓ Pregnancy itself can cause hyperthyroidism, which can eventually lead to a TS. As the circulating estrogen increases during pregnancy, the thyroxine-binding globulin (TBG)

increases. TBG binds to the circulating T4, reducing the free T4 levels. To compensate for this, the size of the thyroid gland increases, and the production of T4 and T3 increases by 50% [15-17]. Owing to the homogeneity of human chorionic gonadotropin (hCG) and TSH, elevated hCG levels can stimulate the thyroid gland, resulting in further elevation of free T4 [17, 18]. Millar *et al.* reported that patients with hyperthyroidism during pregnancy were 10 times more likely to develop a TS than during non-pregnancy [19]. (Discussion - Etiology)

## **Answer to 2<sup>nd</sup> review**

1. The grammar throughout the text can be improved. Examples: “COVID-19 not only can result in significant respiratory symptoms, but also can cause” (abstract) “so the neurologist assessed.” (imaging examinations) and other minor changes in many places.
  - ✓ We have rechecked the text completely, as suggested.
2. **Case presentation:** There is no need to address which findings fit or don't fit with eclampsia in the case description. You should address this issue in the discussion to base your diagnosis.
  - ✓ We have moved the corresponding sentence [from Physical Examination] to the Diagnosis subsection of Discussion.
  - ✓ Because the pregnant woman had seizures, eclampsia was suspected initially. Therefore, it is necessary to identify the symptoms and signs of eclampsia accurately. For example, it is important to identify pretibial pitting edema, visual disturbances, and epigastric pain. In our case, the patient showed no such signs.

**3. Laboratory examinations:**

- the range of values of FT4 and tT3 are different than commonly used, where are they taken from?
  - ✓ The reference ranges were sourced from Williams Obstetrics (25th Edition).
  
- According to which scale do these results reflect a severe hyperthyroidism?
  - ✓ Thank you for this insightful observation. Accordingly, we have changed the wording. We believe that “overt hyperthyroidism” may be more appropriate. (revised severe → overt)
  
- The authors should use the same values of thyroid tests – for example “free thyroxine” is later described as “Free T4”.
  - ✓ We have corrected this point.

**4. Outcome and Follow-up:** what was the condition of the patient at endocrinologist follow-up? Did seizures continue at that time? You should add the values of free T4 and T3 in this section for comparison to the initial values.

- ✓ We have corrected these points.
- ✓ Twelve hours after delivery by cesarean section, the patient's seizures disappeared, and consciousness was restored, as described in Case Summary. Hence, the seizures had ceased by the time the patient was scheduled for a follow-up with the endocrinologist.
- ✓ The patient was then referred to an endocrinologist for evaluation and treatment of hyperthyroidism. In the serological test, TSH ( $<0.01$  mIU/L) was suppressed, but the free T4 (1.86 ng/dL), total T3 (175.3 ng/dL), and TSH receptor antibody (2.44 IU/L; RR: 0.0–1.750 IU/L [6]) were all elevated with respect to the reference values. (Outcome and Follow-Up)

**5. Outcome and follow-up:** to my understanding, the patient got the thyroid-specific treatment only after her symptoms passed and she was stable. This means that the improvement in her condition was spontaneous and can only be related to the delivery of

her baby. Please explain this issue and how it fits with the diagnosis of thyroid storm and not eclampsia.

- ✓ In addition, the patient was normotensive, and there was no proteinuria, fetal growth restriction, thrombocytopenia, kidney failure, hepatic dysfunction, or liver failure. In conclusion, the possibility of eclampsia was judged to be low. (Discussion – Diagnosis)

Do most cases of thyroid storm have a spontaneous resolution?

- ✓ In the case of mild thyrotoxicosis, spontaneous resolution occurs often, but in the case of a thyroid storm, active treatment is required. This has been noted in Discussion - Treatment.
- ✓ Treatment of mild thyrotoxicosis in COVID-19 patients without an underlying thyroid disease does not necessitate thionamides, and most of these patients will recover spontaneously [6]. However, patients with a TS should receive prompt treatment with fluids, antithyroid drugs, steroids, and beta blockers in conjunction with consultation with an endocrinologist. (Discussion – Treatment)

- 6. Discussion:** The authors should further elaborate on the possible inflammatory effect of COVID-19 that caused the thyroid storm. What are other inflammatory-related extrapulmonary manifestations of COVID-19? The authors should address the following article which describes this issue in COVID-19 patients:  
<https://link.springer.com/article/10.1007/s00296-022-05106-3>

- ✓ These suggested points have been added to Discussion - Symptoms.
- ✓ SARS-CoV-2 can also cause a wide variety of extrapulmonary symptoms owing to its inflammatory effects. For example, cardiac (myocarditis, pericardial effusion, shock), renal (glomerulonephritis), hematological (thrombocytopenic purpura, anemia), neurological (Guillain–Barré syndrome, meningoencephalitis, optic neuritis), and musculoskeletal (myositis, arthritis) complications have been reported. [10, 20, 21, 29, 30].

- 7. Discussion (symptoms):** here is the place the authors should elaborate on which symptoms occurred and which not in this case regarding eclampsia and thyroid storm.

- ✓ These points have been added to Discussion - Diagnosis.
- ✓ Because the pregnant woman had seizures, eclampsia was suspected initially. Therefore, it is necessary to identify the symptoms and signs of eclampsia accurately. For example, it is important to identify pretibial pitting edema, visual disturbances, and epigastric pain. In our case, the patient showed no such signs. In addition, the patient was normotensive, and there was no proteinuria, fetal growth restriction, thrombocytopenia, kidney failure, hepatic dysfunction, or liver failure. In conclusion, the possibility of eclampsia was judged to be low. (Discussion - Diagnosis)

## ANSWER

- The authors write that the patient's disease severity was severe and use the clinical improvement scale. However, according to the accepted severity scale – COVID-19 requiring mechanical ventilation is part of a critical disease severity.

<https://www.acep.org/corona/covid-19-field-guide/diagnosis/diagnosis-when-there-is-no-testing/>

- ✓ **We revised it as you pointed out.**
- ✓ **According to the widely accepted severity scale of COVID-19, illness of severity was critical requiring mechanical ventilation [5]. (*History of present illness*)**

- Once again, I highly recommend the authors to address the following article which describes the extra-pulmonary involvement of COVID-19 in more than one system concurrently and addresses the possible inflammatory mechanism of extra-pulmonary COVID-19 like the authors do in their paper. <https://link.springer.com/article/10.1007/s00296-022-05106-3>

- ✓ **We revised it as you pointed out.**
- ✓ **I reviewed the paper you recommended and added it to the reference list. (reference #31)**

- I would like to address the differential diagnosis of eclampsia.

- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3119563/>)

Many cases of eclampsia even most cases in some studies present without HTN or proteinuria.

- ✓ **There is eclampsia without high blood pressure or proteinuria. When diagnosing eclampsia in clinical practice, several clinical aspects are evaluated together. In our case, there was no finding corresponding to eclampsia other than seizure.**



Regardless of the other differential diagnosis, the patient improved without any

Thyroid-specific treatment while the authors clearly state that her condition was severe hyperthyroidism that is not likely to improve without and where treatment should be given promptly.

- ✓ **Treatment of mild thyrotoxicosis in COVID-19 patients without an underlying thyroid disease does not necessitate thionamides, and most of these patients will recover spontaneously [6]. However, patients with a TS should receive prompt treatment with fluids, antithyroid drugs, steroids, and beta blockers in conjunction with consultation with an endocrinologist. (*Discussion – treatment*)**
- ✓ **After delivery by cesarean section, the intensity of the seizures decreased but persisted. Therefore, low-level sedation was maintained with midazolam for about 12 hours in the intensive care unit. Over time, the intensity of the seizures decreased, and consciousness was restored. (*outcome and follow-up*)**
- ✓ **The reason why the patient's consciousness was restored and seizure decreased despite not performing a thyroid specific treatment (antithyroid drug-methimazole) was due to the reduction of physiological burden due to the termination of pregnancy (cesarean section). In our case, methimazole was administered after cesarean section and consciousness was restored.**

Moreover, there were no symptoms before or after the seizures related to hyperthyroidism – such as irritability, heat sensitivity, palpitations, and so on.

- ✓ **Vital signs revealed a blood pressure of 121/71 mmHg and heart rate of 115 beats per minute. (*Physical examination*)**