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## Hydatidiform mole in the era of COVID-19 pandemic. Is there an association?

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In March 2020, the World Health Organization considered coronavirus disease-2019 (COVID-19) as a worldwide pandemic.<sup>1</sup> Hydatidiform mole (HM) is a non-malignant form of gestational trophoblastic diseases (GTDs) characterized by failure of fetal development and over proliferation of the trophoblasts.<sup>2</sup> In our tertiary care Obstetric hospital, we observed a rising incidence of cases diagnosed with HM in synchronization with the onset of COVID-19 pandemic. Most of cases were primigravidae with no other known risk factors for HM. We tried to put possible explanations for this condition based on the immunological and laboratory parameters of COVID-19 disease.

Previous researches on the pathogenesis of recurrent HMs detected some mutations in NLRP7 protein, that has a role in pathogen mediated inflammation and apoptosis.<sup>3</sup> This increases the possibility that variable viral, bacterial and parasitic infections can mediate HM.

In HM, there is a Lower white blood cell levels compared to healthy pregnancy that reflects the association of HM with a poorer inflammatory function enhancing trophoblastic invasion.<sup>4</sup> Additionally, in patients with GTDs, there was a significant decrease in the percentage and absolute counts of lymphocytes.<sup>5</sup> Interestingly, positive COVID-19 patients showed, as GTDs patients, leucopenia as one of the important parameters in H-score for secondary haemophagocytic lymphohistiocytosis which occur mainly in adults by viral infections.<sup>6</sup> This could explain the causative association of COVID-19 in the pathogenesis of HM.

Previous studies showed that activation of endometrial lymphocytes and macrophages can produce a negative environment affect the implanting embryo. One of the causative factors for activation is the non-reproductive tissue specific antigens such as those of infectious organisms.<sup>7</sup> This activation will lead to release of variable cytokines including interleukin 1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interferon  $\alpha$  and  $\gamma$  (IFN $\alpha$ ,  $\gamma$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).

Therefore, these cytokines may be used as valuable biomarkers in the diagnosis of GTDs as they have a definite role in its pathogenesis. COVID-19 is characterized by increased IL-2, IL-7, granulocyte colony stimulating factor, interferon- $\gamma$  inducible protein 10, and TNF- $\alpha$ .<sup>6</sup> This increases the interest that raised cytokines levels in COVID-19 patients may affect the normal implantation leading to development of HM.

Despite the fact that HM is multifactorial in its etiology, we still have limited knowledge about its immunological aspects. Further studies are recommended to show the COVID-19 contribution to the pathogenesis of HM. Till that, we suggest that obstetricians advise pregnant women with HM that they could have COVID-19 disease, and those patients could be referred to perform COVID-19 testing through nasopharyngeal swab.

**Conflict of interest:**

The authors state that there are no conflicts of interest.

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