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Apropos of menstrual changes and abnormal uterine bleeding after COVID-19 vaccination

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A R T I C L E   I N F O

Article history:
Received 1 November 2022
Accepted 3 November 2022
Available online xxxx

Keywords:
Coronavirus disease 2019 (COVID-19)
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
COVID-19 vaccination
Menstrual changes
Heavy menstrual bleeding
Abnormal uterine bleeding
Adenohypophysis microcirculation
Fenestrated capillaries

A B S T R A C T

It is news of 28 October 2022 that the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency has recommended to add heavy menstrual bleeding among the side effects of unknown frequency inside the package insert of nucleoside-modified messenger ribonucleic acid (modRNA) vaccines to prevent coronavirus disease 2019 (COVID-19). The decision has been made in the light of the numerous reports of unexpected menstrual changes or abnormal uterine bleeding following COVID-19 vaccination. Here we advance a possible involvement of the particular adenohypophyseal microcirculation in these strange and still unexplained events.

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It is news of 28 October 2022 that the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended to add heavy menstrual bleeding among the side effects of unknown frequency inside the package insert of nucleoside-modified messenger ribonucleic acid (modRNA) vaccines to prevent coronavirus disease 2019 (COVID-19), the ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1–2 Previously, we have pointed out the numerous reports of unexpected menstrual changes or abnormal uterine bleeding following COVID-19 vaccination recorded on the United Kingdom “Yellow Card” surveillance system.3 In this regard, we have described a similar case of amenorrhea due to hyperprolactinemia in a 28-year-old Caucasian female with pituitary apoplexy (PA) accompanied by de novo headache, temporally after adenoviral vector-based COVID-19 vaccination.3 To complete this clinical case, we here specify the full absence of SARS-CoV-2 infection by molecular swab, of visual disturbance by ophthalmologic investigation, of micro-/macroadenoma by cerebral imaging (performed only after the second dose when the patient came to our attention), and of cardiovascular risk factors, such as diabetes, arterial hypertension, hyperlipidemia, atrial fibrillation, smoking and anti-contraceptive pill. All these additional data allow us to advance a possible alternative explanation for PA and transient menstrual changes concerning with an acute microvascular damage. In fact, the particular microcirculatory apparatus of the adenohypophysis consists of a rich network of fenestrated capillaries which account for the high metabolic exchanges of the gland, strictly dependent on the hypothalamus by feedback mechanism [Fig. 1]. It is known that the main arterial supply for the adenohypophysis is represented by the two superior hypophyseal arteries; the branches of each artery terminate in a primary capillary plexus, which allows for the rapid passage of hypothalamic-releasing hormones and inhibitory factors into the hypophyseal portal system.4–5 Once the blood reaches the adenohypophysis, it spreads within a secondary capillary plexus precisely consisting of fenestrated capillaries, in direct contact with the secretory cells [Fig. 1]. The main venous return is towards the cavernous sinus, but supplementary collaterals are connected with the hypothalamus’ basis, allowing a direct arrival of blood enriched with pituitary hormones to the hypothalamus.4 Given that COVID-19 can
rarely complicate with pituitary apoplexy and that any vaccination represents an attenuated form of the disease by definition,\textsuperscript{3} a resulting hypercoagulative state may rarely occur and involve fenestrated capillaries, where the blood flow is significantly decelerated.\textsuperscript{6–8} The pre-existing interconnected small branches and the trans-sellar arterial blood supply usually are sufficient collaterals,\textsuperscript{9} but sometimes they could be inadequate to the high blood demand from the pituitary gland, thus promoting the onset of microischemic events and subsequent menstrual abnormalities.\textsuperscript{10}

**Declaration of Competing Interest**

The authors declare no competing interest.

**Acknowledgments**

The authors thank the neuropathologist Dr. Elena Zunarelli, MD for her help in retrieving the histological material.

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