Received: 11 March 2021 | Accepted: 13 April 2021 | First published online: 13 May 2021

DOI: 10.1002/ijgo.13719

BRIEF COMMUNICATION

Obstetrics

Premature ovarian insufficiency secondary to COVID-19 infection: An original case report

James Wilkins | **Shamma Al-Inizi**

Department of Obstetrics and Gynecology, South Tyneside & Sunderland Royal Hospital, South Shields, UK

Correspondence
James Wilkins, Department of Obstetrics and Gynecology, South Tyneside & Sunderland Royal Hospital, South Shields, NE34 0PL, UK.
Email: james.wilkins2@nhs.net

Keywords: COVID-19, premature ovarian insufficiency, subfertility

Coronavirus disease 2019 (COVID-19) causes some people to develop severe disease associated with acute respiratory distress syndrome, hypercoagulability, and neurological disease amongst other complications.[1] There is increasing recognition that a proportion of patients who contract this acute infection will develop a subsequent long-term illness termed 'long-COVID,' thought to be secondary to chronic tissue inflammation. There is a risk that reproductive tissue may also be vulnerable, potentially resulting in subfertility; however, to date no cases of deranged ovarian function secondary to COVID-19 have been reported.

A 34-year-old patient presented to our fertility clinic in November 2020 with primary subfertility after having regular unprotected sexual intercourse for over 1 year. She and her partner were investigated for this and she was found to have developed premature ovarian insufficiency with high gonadotrophin levels and a very low progesterone level of 0.3 nmol/L. The common causes of this were investigated but none were identified. She was a non-smoker with a healthy body mass index, and had undergone neither pelvic surgery nor chemo/radiotherapy previously. In terms of comorbidities, she was fit and well except for controlled hypothyroidism which was medicated with levothyroxine with a recent thyroid stimulating hormone of 0.98 mUI/L, which is within the normal range.

The patient was diagnosed with COVID-19 in April 2020 by a nasopharyngeal swab demonstrating positive viral serology. During the acute illness she developed symptoms of shortness of breath, fatigue, myalgia, and headache, but did not require hospitalization nor active treatment for these symptoms. Her shortness of breath improved over the course of 2–3 weeks but she experienced persistent fatigue and continuing myalgia over the next few months. Due to this, the patient has been referred to the long-COVID clinic. In addition, the patient's periods became irregular with oligomenorrhea and she began to experience regular hot flushes and night sweats. Two months prior to contracting COVID-19, in February 2020, she had normal regular periods and normal gonadotrophin levels: follicule stimulating hormone (FSH) 8 U/L and luteinizing hormone (LH) 2 U/L; however, in November 2020, 7 months after her acute infection, her FSH was 78 U/L and LH 43 U/L and on repeat 2 months later her gonadotrophins were persistently raised (FSH 89 U/L and LH 32 U/L).

These events mean that the patient is very unlikely to fall pregnant without support and the available methods for attempting conception are assisted reproduction with oocyte donation or adoption, hence a referral to the local in vitro fertilization center was arranged.

Due to the novel nature of this presentation, written consent to publish this case was obtained from the patient.

It is well established that viruses can cause inflammation of reproductive tissue; indeed, one of the most common clinical manifestations of mumps is orchitis, which can be damaging to testicular function. Furthermore, several case reports have discussed the development of orchitis in patients who have contracted COVID-19 and small studies have shown pathological changes to testicular tissue.[2] A possible mechanism for this is expressed in Figure 1. Reproductive tissue expresses the ACE2 receptor and COVID-19 may utilize this to gain cellular entry.[3] Viral entry to these cells would promote an inflammatory response through the complement cascade and associated chemotaxis, phagocytosis of infected cells, and antigen presentation causing local T cell activation and cytokine release.[4] These effects have the potential to cause significant cellular demise either directly through apoptosis and phagocytosis or indirectly through mechanisms such as the disruption of tissue microvasculature.[4] These could cause sufficient damage to impair steroidogenesis and ovulation, thus affecting fertility.

To date studies have not found histological damage to ovarian tissue following infection with COVID-19, nor have case reports

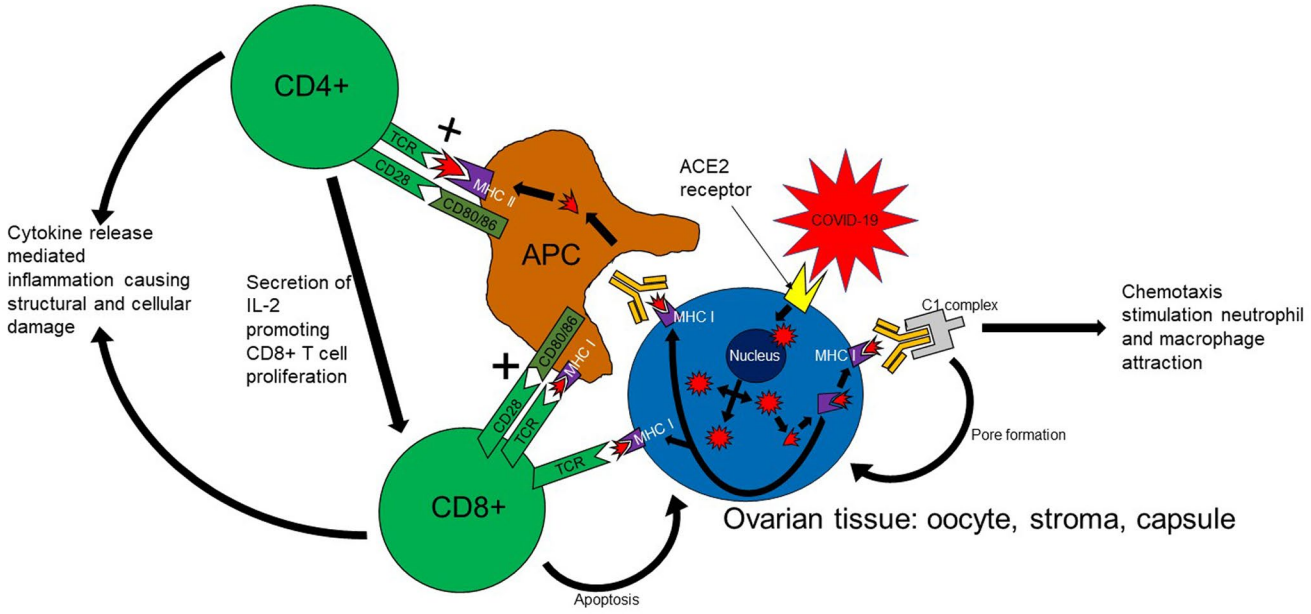

FIGURE 1 Possible mechanism of COVID-19 induced premature ovarian insufficiency

described an effect of COVID-19 on female fertility. This may be due to several factors. Firstly, the ACE2 receptor is less expressed in ovarian tissue compared to testicular tissue[3] meaning the chance of viral invasion to this tissue and subsequent damage may be less. Additionally, very few studies have examined ovarian tissue following COVID-19 meaning viral-associated damage may have thus far gone undetected. Furthermore, investigation of subfertility is normally only undertaken following a minimum of 1 year of regular unprotected sex. As the pandemic began to spread worldwide in early 2020, it is likely that if COVID-19 were to have an impact the ovarian function of a significant proportion of women, then the impact of this would not be investigated until early 2021 and therefore would not begin to be apparent until this time. The possibility that a cohort of women may have contracted thus far undiagnosed COVID-19-induced subfertility, with more at risk of developing this, means that health professionals working in fertility should be highly alert to this potentiality and more work should be performed to investigate this further.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

JW assessed the patient about whom this case report is detailed in clinic alongside SAI and, following this, planned this case report, assessed the background literature and hypothesized a potential mechanism for the association described. Following this, JW wrote up this work with contributions from SAI. SAI was the primary assessor of the patient in her subfertility clinic and suggested the case would merit publication, encouraging JW with this. SAI then reviewed the work produced by JW making changes and suggestions as appropriate in the writing up process before giving her approval for submission. Both authors contributed to and approved of the final version of this manuscript.

ORCID

James Wilkins https://orcid.org/0000-0003-0580-0608

REFERENCES

1. Public Health England. *COVID-19: Epidemiology, Virology and Clinical Features*. London, UK: Public Health England; 2021.
2. Madjunkov M, Dviri M, Librach C. A comprehensive review of the impact of COVID-19 on human reproductive biology, assisted reproduction care and pregnancy: a Canadian perspective. *J Ovarian Res*. 2020;13(1):140.
3. Hikmet F, Méar L, Edvinsson Å, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol*. 2020;16(7):e9610.
4. Murphy K, Weaver C. *Janeway's Immunobiology*. 9th ed. New York: W. W. Norton & Company; 2017.