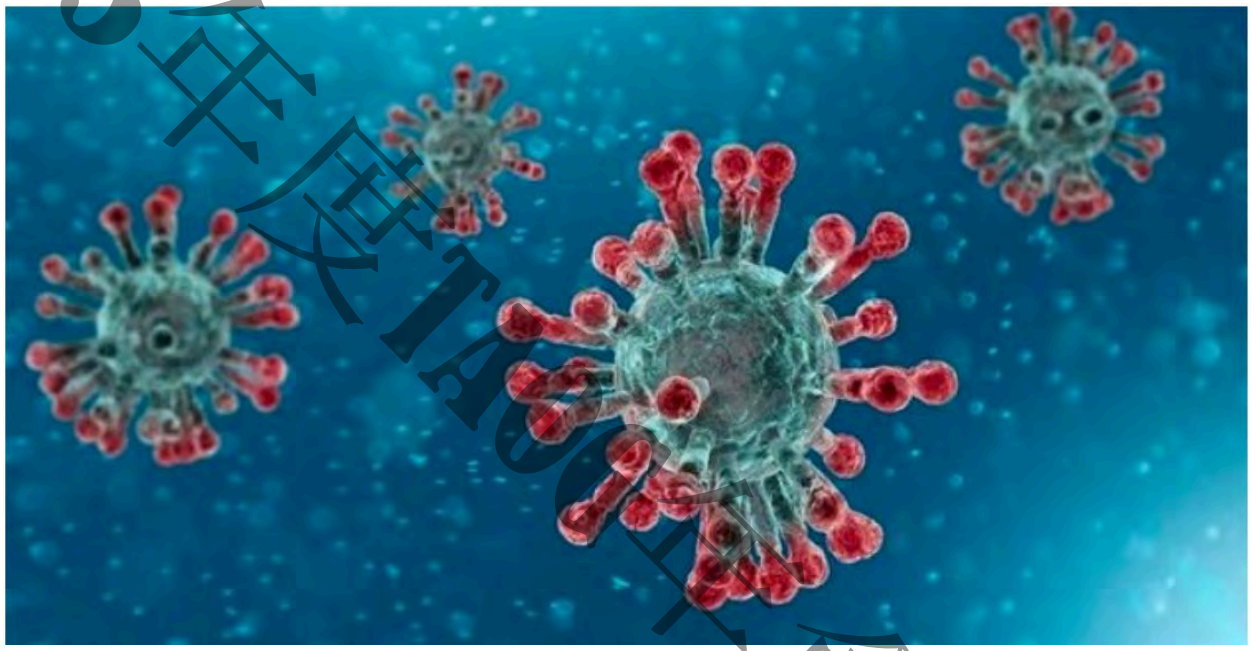
Ovarian function after COVID-19



國泰綜合醫院婦產科

賴宗炫

台灣婦產科醫學會 2024年會
2024/03/10 15:30-16:00
圓山飯店12樓崑崙廳

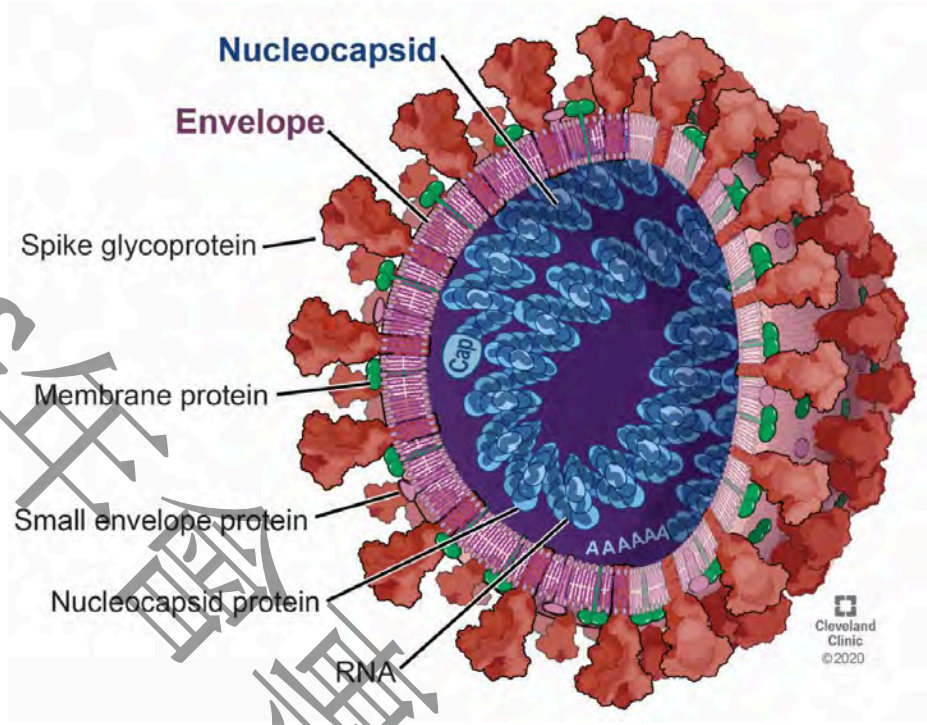
Outlines

1. Introduction
2. The possible mechanisms of SARS-CoV-2 infection on female fertility
3. The clinical presentations of ovarian dysfunction during and after SARS-CoV-2 infection
4. Long COVID-19 on ovarian function and female fertility
5. COVID-19 vaccination on ovarian function and female fertility
6. Take home message

SARS-CoV-2

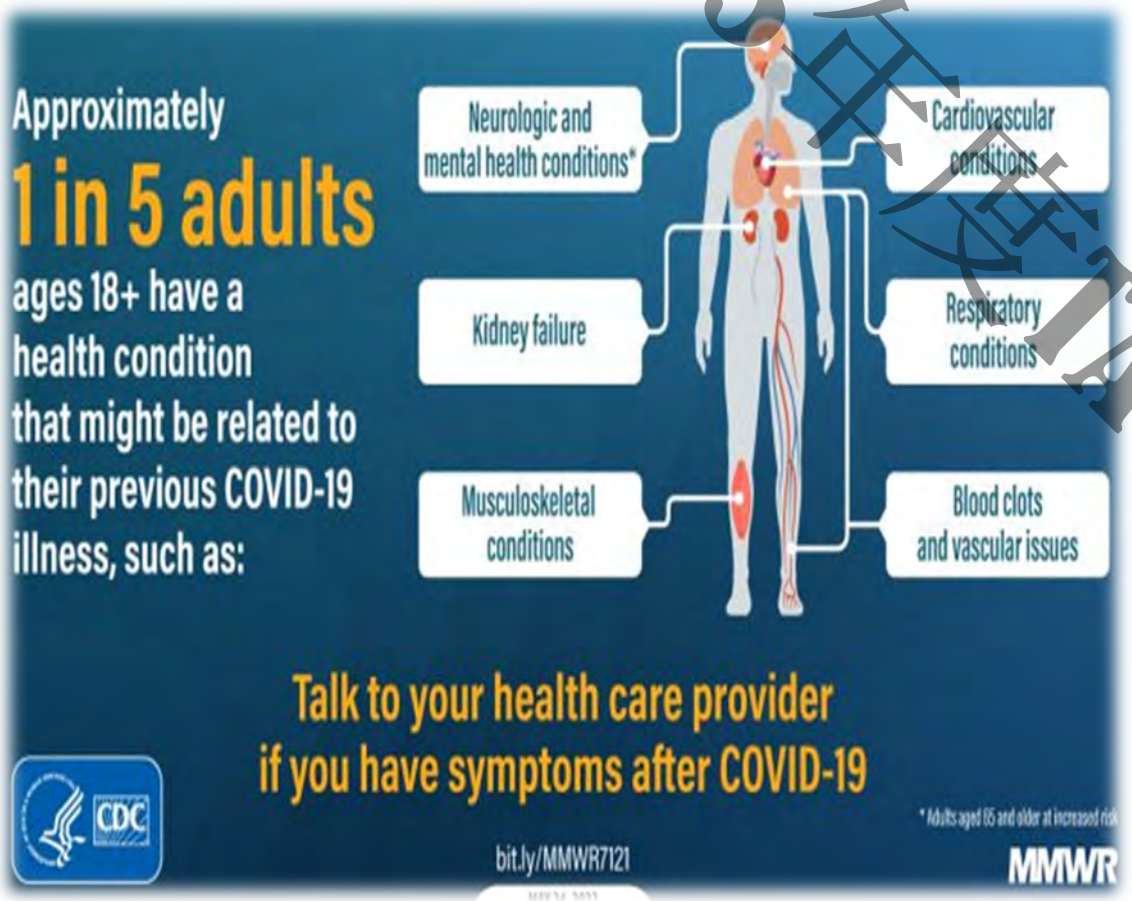
SARS-CoV-2 is the virus that causes coronavirus disease 2019 (COVID-19)
SARS = severe acute respiratory distress syndrome

- Sars-CoV-2屬冠狀病毒科之betacoronavirus。
- 有外套膜之單股正鏈RNA病毒。
- 引起人類和脊椎動物的疾病，屬於人畜共通傳染疾病。
- 已知會感染人類的七種冠狀病毒: 包括alpha亞科的HCoV-229E病毒與HCoV-NL63病毒，以及beta亞科的HCoV-HKU1病毒、HCoV-OC43病毒、重急性呼吸道症候群冠狀病毒（SARS-CoV）、中東呼吸症候群冠狀病毒（MERS-CoV）和最新發現的新型冠狀病毒SARS-CoV-2。
- 以呼吸道症狀為主，包括鼻塞、流鼻水、咳嗽、發燒等一般上呼吸道感染症狀，但嚴重急性呼吸道症候群冠狀病毒（SARS-CoV）、中東呼吸症候群冠狀病毒（MERS-CoV）與新型冠狀病毒SARS-CoV-2感染後比一般人類冠狀病毒症狀嚴重，部分個案可能出現嚴重的肺炎與呼吸衰竭等。

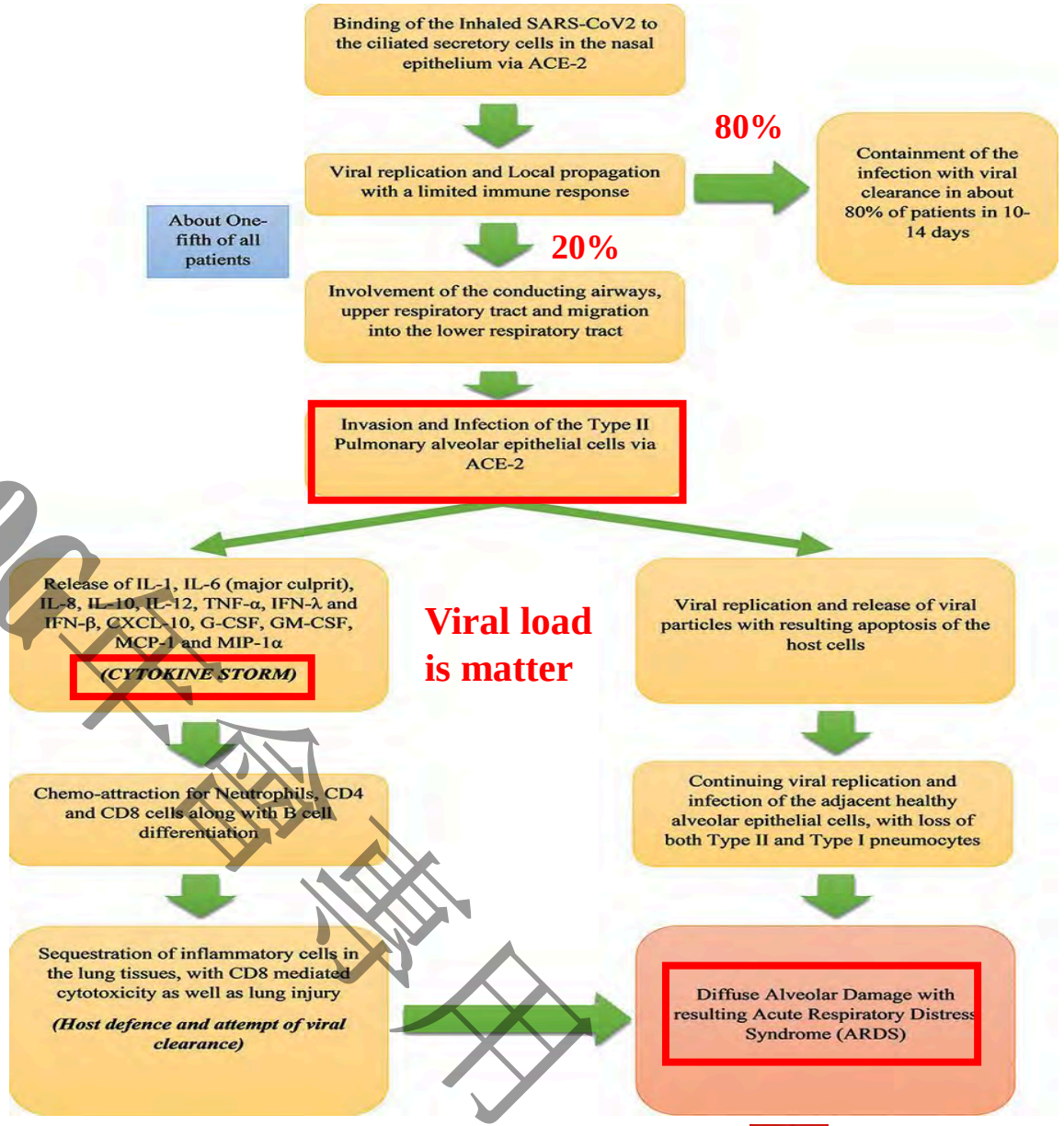


Cornelia C. Bergmann, and Robert H. Silverman CCJM 2020;87:321-327

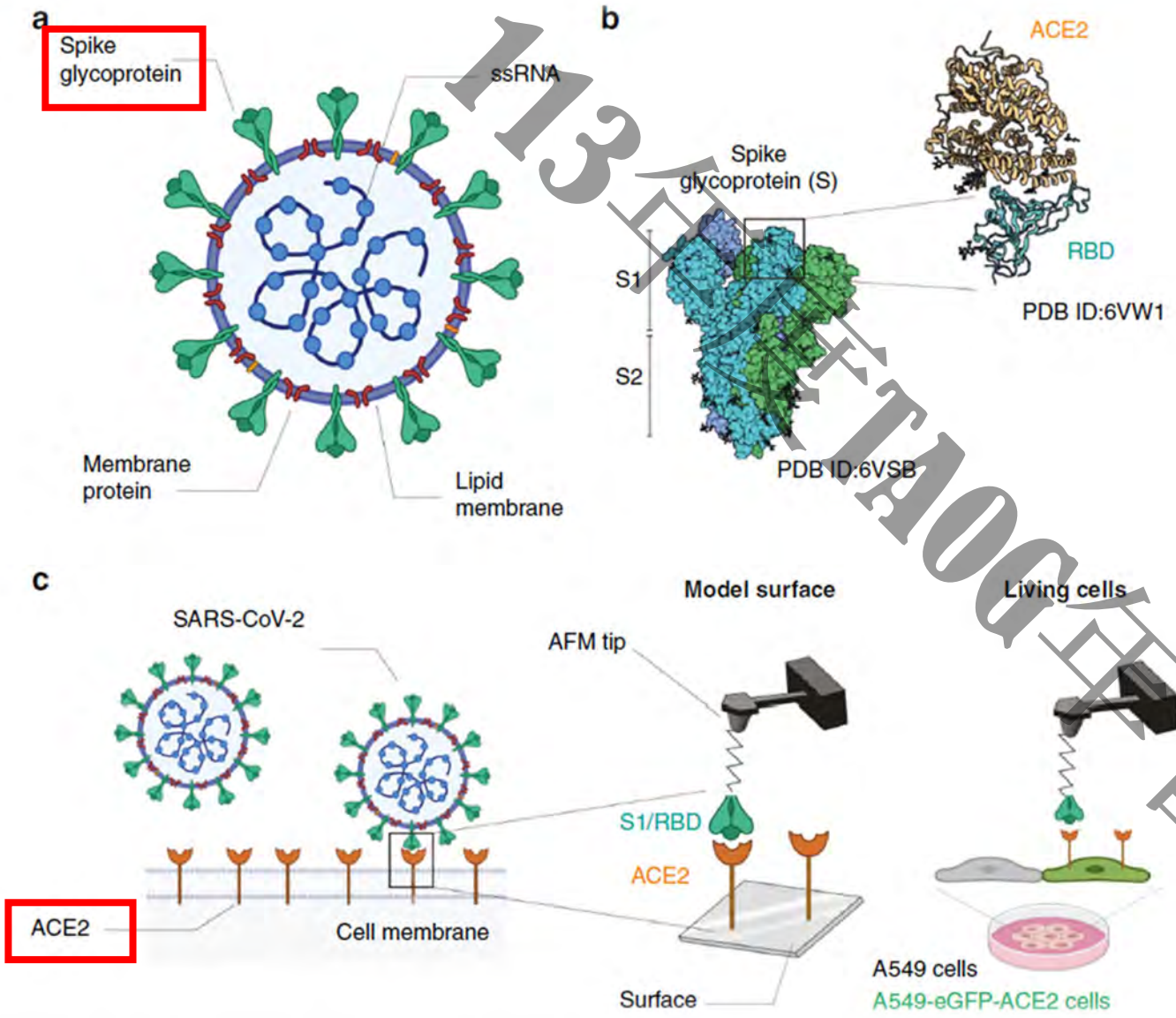
Pathophysiology of COVID-19



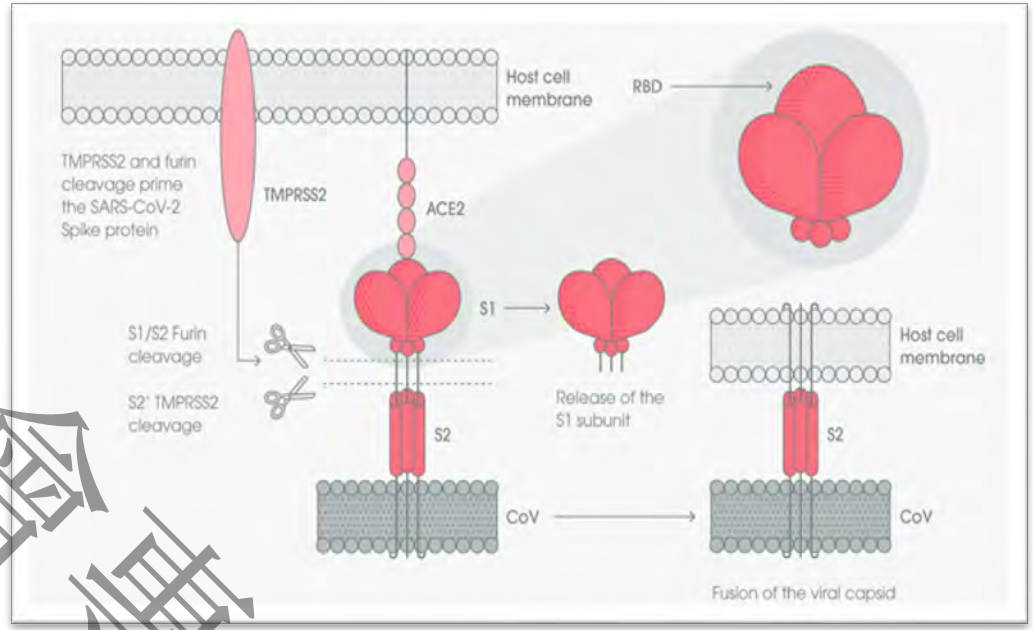
新光醫院李毅評主任提供



Anant Parasher Postgrad Med J 2021;97:312-320 PMJ



《Cell. 2020 Apr 16;181(2):271-280》

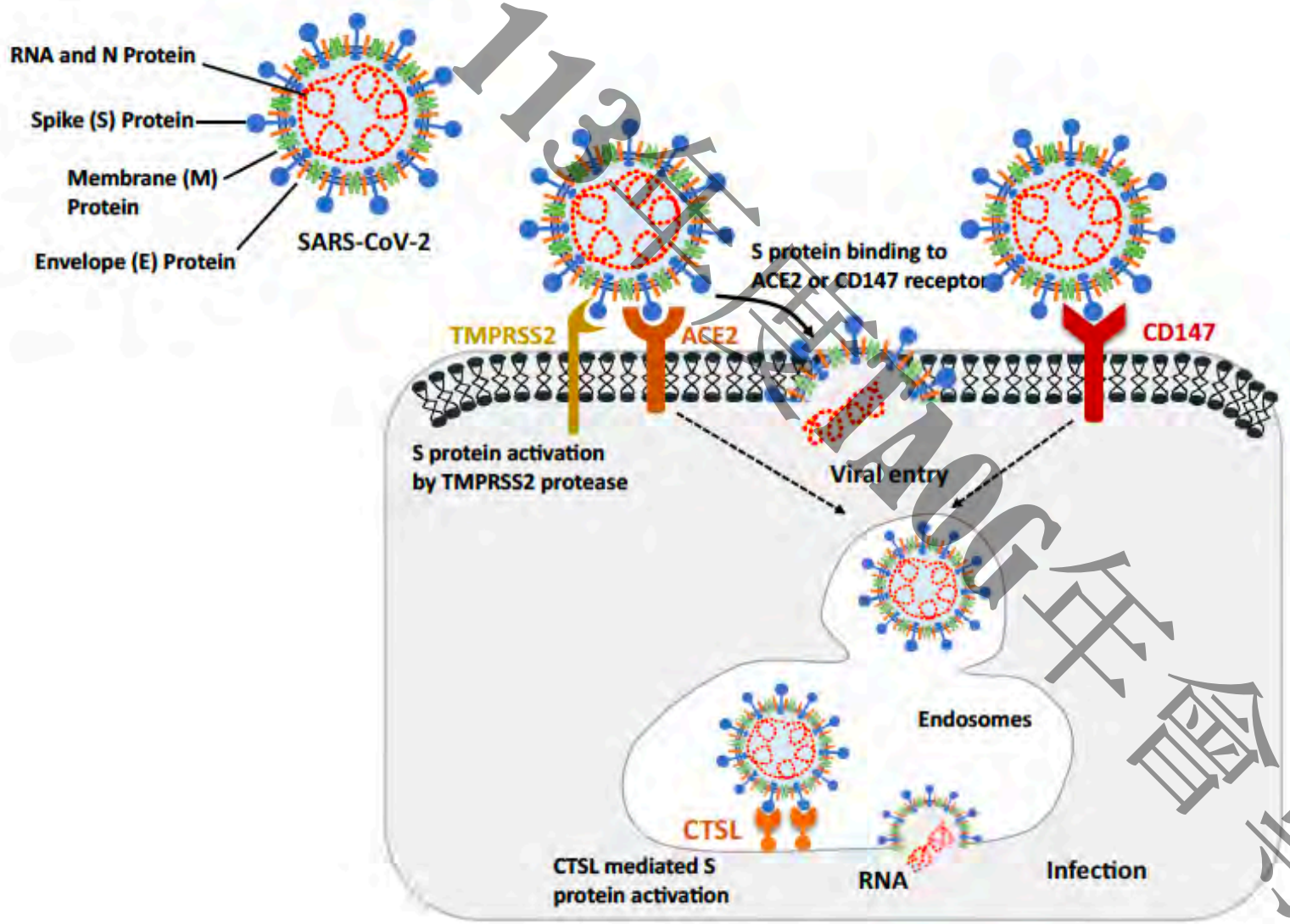


《Life Sci Alliance. 2020 Jul 23;3.》

新光醫院李毅評主任提供

Two ways to entry:

1. Membrane fusion-
   ACE2 + TMPRSS2
2. Endocytosis-
   CD147 + CTSL



Rajput. SARS-CoV-2 receptors on human embryos. Fertil Steril Sci 2021.

Outlines

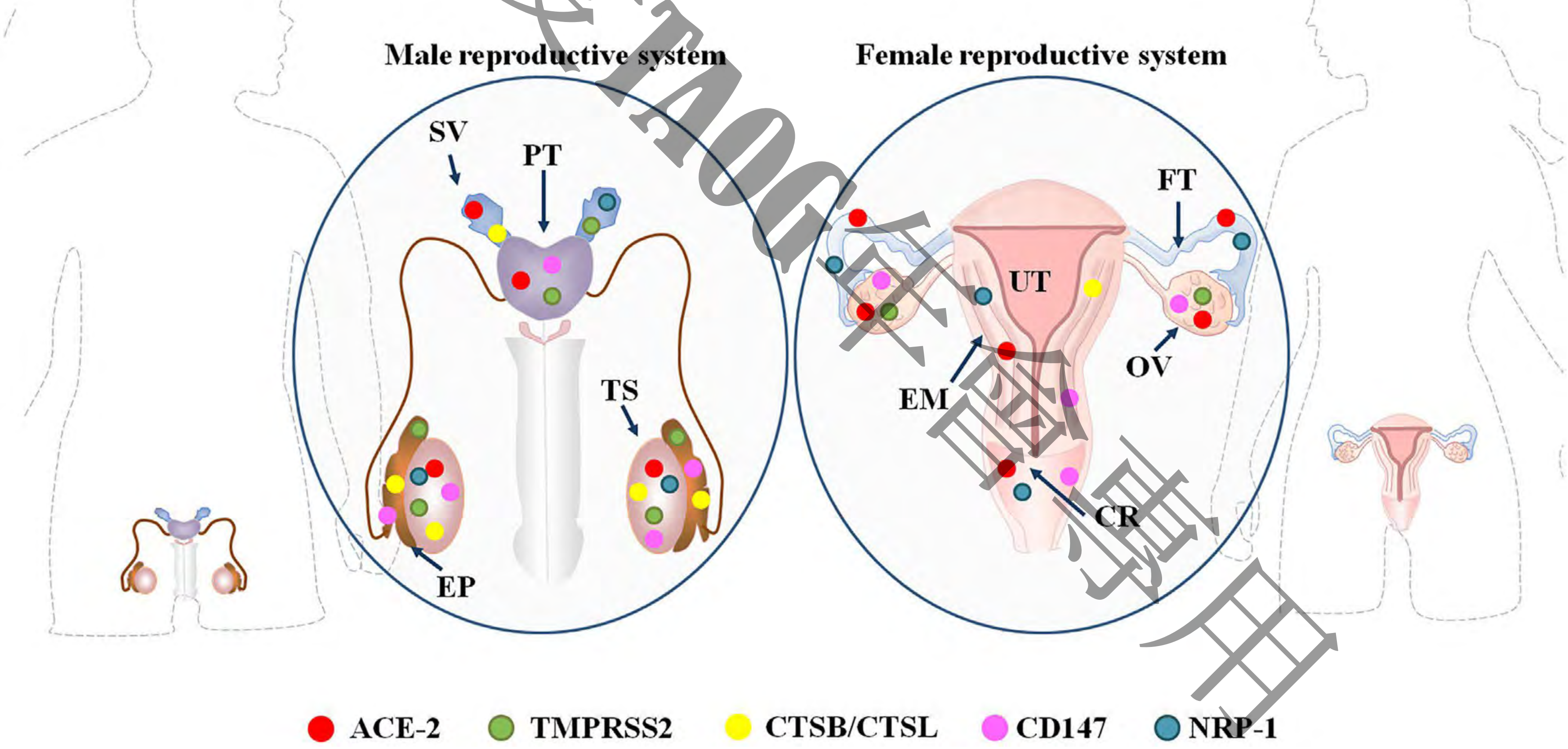
1. Introduction
2. The possible mechanisms of SARS-CoV-2 infection on female fertility
3. The clinical presentations of ovarian dysfunction during and after SARS-CoV-2 infection
4. Long COVID-19 on ovarian function and female fertility
5. COVID-19 vaccination on ovarian function and female fertility
6. Conclusion

ELSEVIER

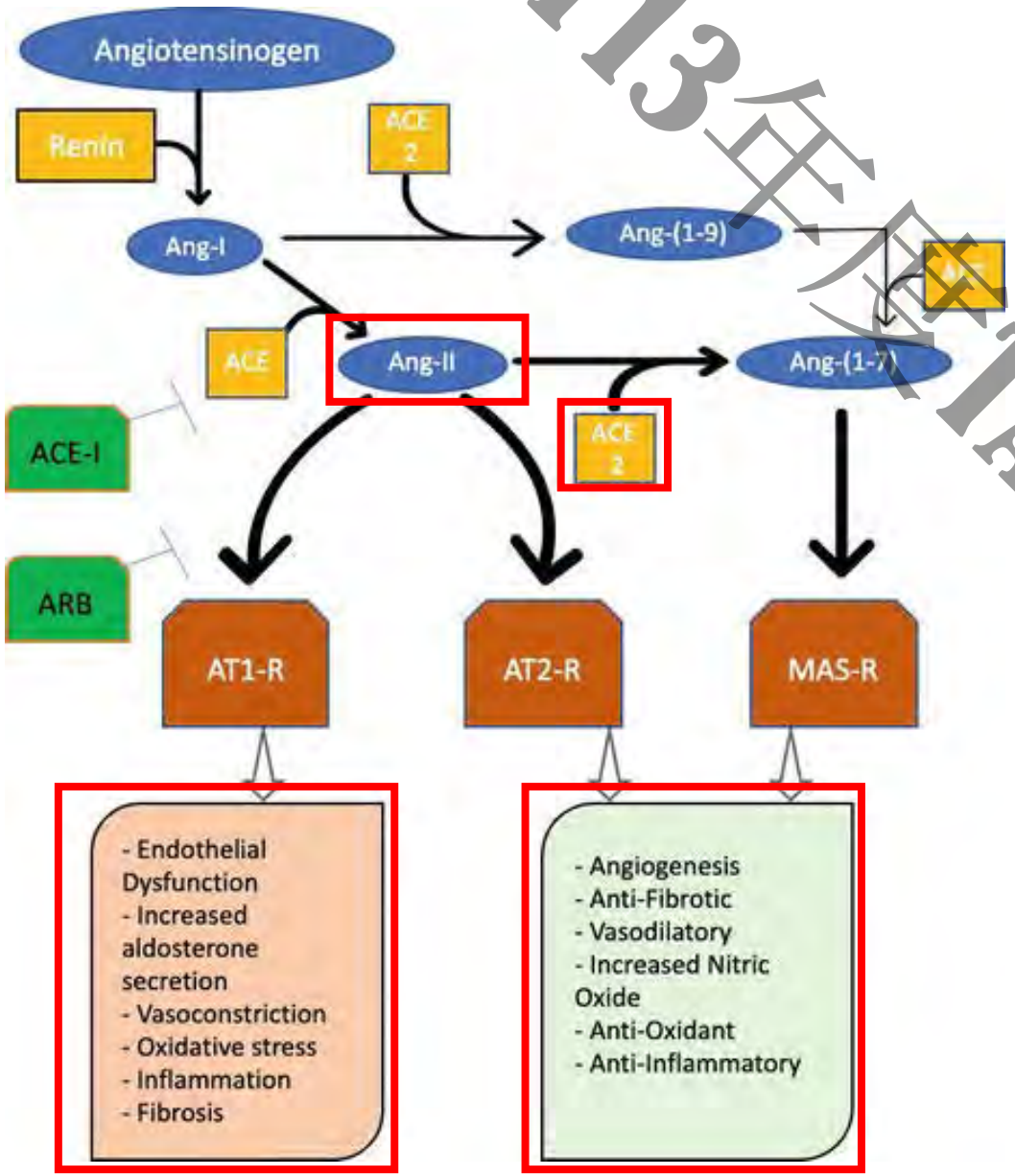
Understanding the cross-talk between mediators of infertility and COVID-19

Prem Rajak[a,*], Sumedha Roy[b], Moumita Dutta[c], Sayanti Podder[d], Saurabh Sarkar[e], Abhratanu Ganguly[f], Moutushi Mandi[g], Salma Khatun[h]

[a] Department of Animal Science, Kazi Nazrul University, Asansol, West Bengal, India
[b] Department of Biomolecular Medicine, Faculty of Medicine and Health Sciences, Ghent University, Belgium
[c] Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA
[d] Post Graduate Department of Zoology, Modern College of Arts, Science and Commerce, Ganeshkhind, Pune, Maharashtra, India
[e] Department of Zoology, Gushkara Mahavidyalaya, Gushkara, Purba Bardhaman, West Bengal, India
[f] Post Graduate Department of Zoology, A.B.N. Seal College, Cooch Behar, West Bengal, India
[g] Toxicology Research Unit, Department of Zoology, The University of Burdwan, Purba Bardhaman, West Bengal, India
[h] Department of Zoology, Krishna Chandra College, Hetampur, West Bengal, India

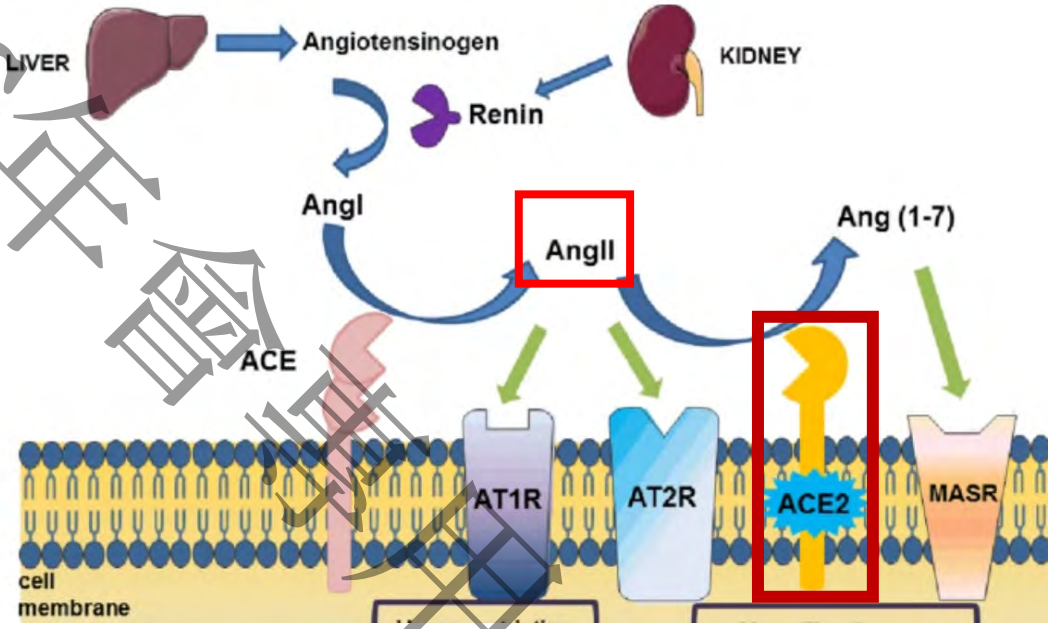


Renin-Angiotensin system (RAS)



ACE2 is crucial for regulation of the RAS expressed mainly in the respiratory tract, intestine, heart, kidney and endothelium.

ACE: Angiotensin converting enzyme
ACE2: Angiotensin converting enzyme 2
Ang I: Angiotensin I
Ang II: Angiotensin II
AT1-R: Angiotensin II receptor type I
AT2-R: Angiotensin II receptor type II



(Violeta et al., 2021)

Angiotensin-(1-7), its receptor Mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary

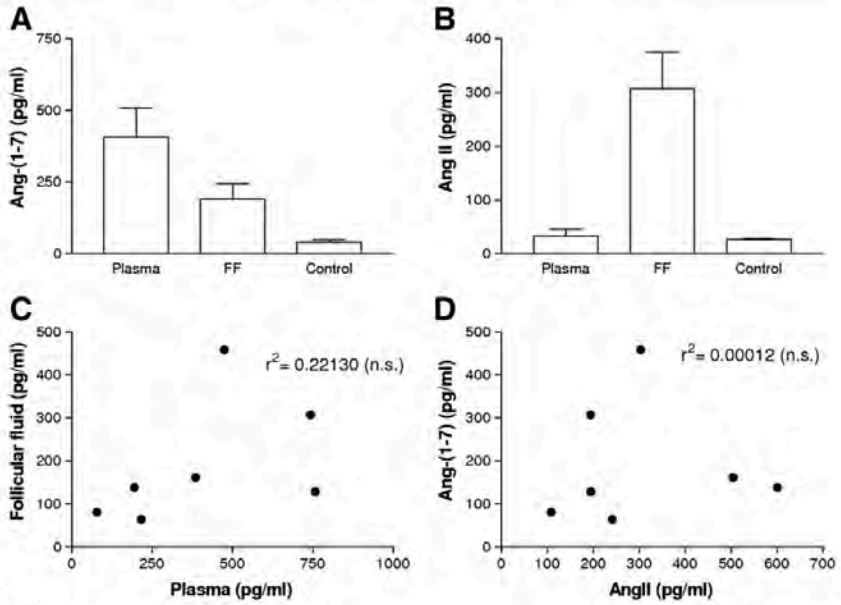
Fernando M. Reis, M.D., Ph.D.,[a,b] *Daniela R. Bouissou, M.D.,*[a] *Virginia M. Pereira, Ph.D.,*[c] *Aroldo F. Camargos, M.D., Ph.D.,*[a] *Adelina M. dos Reis, Ph.D.,*[b,c] *and Robson A. Santos, M.D., Ph.D.*[c]

[a] Department of Obstetrics and Gynecology, Federal University of Minas Gerais; [b] National Institute of Hormones and Women's Health; and [c] Department of Physiology and Biophysics, Federal University of Minas Gerais, Belo Horizonte, Brazil

Objective: To investigate whether angiotensin (Ang)-(1-7), its receptor Mas, and angiotensin-converting enzyme type 2 (ACE2) are present in human ovary.
Design: Cross-sectional study.
Setting: Academic hospital.
Patient(s): Twelve reproductive-age women and five postmenopausal women undergoing oophorectomy for nonovarian diseases and seven women having controlled ovarian hyperstimulation for IVF.
Intervention(s): Ovarian tissue was obtained from the reproductive-age women and postmenopausal women undergoing oophorectomy for nonovarian diseases. Follicular fluid (FF) samples were obtained from the women having controlled ovarian hyperstimulation for IVF.
Main Outcome Measure(s): Localization of Ang-(1-7) and Mas by immunohistochemistry; measurement of Ang-(1-7) in ovarian FF by RIA; detection of messenger RNAs encoding Mas and ACE2 with use of real-time polymerase chain reaction; assessment of ^{125}I-labeled Ang-(1-7) binding to ovarian sections with use of autoradiographic binding assay.
Result(s): Angiotensin-(1-7) and the receptor Mas were localized to primordial, primary, secondary, and antral follicles, stroma, and corpora lutea of reproductive-age ovaries. Postmenopausal women expressed both the peptide and its receptor in the ovarian stroma. Angiotensin-(1-7) was detectable in FF (mean ± SE: 191 ± 54 pg/mL). Both Mas and ACE2 messenger RNAs were expressed in ovarian tissue, as revealed by real-time polymerase chain reaction, and ovarian binding sites for ^{125}I-labeled Ang-(1-7) were identified by autoradiography.
Conclusion(s): Angiotensin-(1-7), its receptor Mas, and ACE2 are expressed in the human ovary. The peptide is present in several ovarian compartments and can be quantified in FF. (Fertil Steril® 2011;95:176–81. ©2011 by American Society for Reproductive Medicine.)

Key Words: Ovary, angiotensin-(1-7), Mas, renin-angiotensin system, follicular fluid

Angiotensin-(1-7) and Ang-II concentrations in plasma and FF from gonadotropin-stimulated and unstimulated *(Control)* patients. **A,** Ang-(1-7) concentration. **B,** Ang II concentration. **C,** Lack of linear correlation between plasma and FF Ang-(1-7) concentrations. **D,** Lack of linear correlation between FF Ang-(1-7) and Ang II concentrations. n.s. = not significant.



Reis. Angiotensin-(1-7) and Mas receptor in the human ovary. Fertil Steril 2011.

1. ACE2 and Mas are expressed in human ovaries.
2. Ang (1-7) and Mas co-localized to primodial, primary, secondary, and antral follicles and were present in the stroma and corpora lutea of human reproductive-aged ovaries.
3. Ang (1-7) was also detectable in follicular fluid.

Fertil Steril® 2011;95:176–81.

Coronavirus disease-19 and fertility: viral host entry protein expression in male and female reproductive tissues

Kate E. Stanley, B.A,[a] Elizabeth Thomas, B.A.,[a] Megan Leaver, M.Sc.,[a] and Dagan Wells, Ph.D.[a,b]

[a] Nuffield Department of Women's and Reproductive Health, University of Oxford, John Radcliffe Hospital, Women's Centre, Oxford; and [b] Juno Genetics, Winchester House, Oxford Science Park, Oxford, United Kingdom

Objective: To identify cell types in the male and female reproductive systems at risk for SARS-CoV-2 infection because of the expression of host genes and proteins used by the virus for cell entry.
Design: Descriptive analysis of transcriptomic and proteomic data.
Setting: Academic research department and clinical diagnostic laboratory.
Patient(s): Not applicable (focus was on previously generated gene and protein expression data).
Intervention(s): None.
Main Outcome Measure(s): Identification of cell types coexpressing the key angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) genes and proteins as well as other candidates potentially involved in SARS-CoV-2 cell entry.
Result(s): On the basis of single-cell RNA sequencing data, coexpression of ACE2 and TMPRSS2 was not detected in testicular cells, including sperm. A subpopulation of oocytes in nonhuman primate ovarian tissue was found to express ACE2 and TMPRSS2, but coexpression was not observed in ovarian somatic cells. RNA expression of TMPRSS2 in 18 samples of human cumulus cells was shown to be low or absent. There was general agreement between publicly available bulk RNA and protein datasets in terms of ACE2 and TMPRSS2 expression patterns in testis, ovary, endometrial, and placental cells.
Conclusion(s): These analyses suggest that SARS-CoV-2 infection is unlikely to have long-term effects on male and female reproductive function. Although the results cannot be considered definitive, they imply that procedures in which oocytes are collected and fertilized in vitro are associated with very little risk of viral transmission from gametes to embryos and may indeed have the potential to minimize exposure of susceptible reproductive cell types to infection in comparison with natural conception.
(Fertil Steril® 2020;114:33-43. ©2020 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: COVID-19, fertility, testis, ovary, IVF

Single-cell RNA sequencing data:

1. Oocyte was found to express ACE2 and TMPRSS2, but coexpression was not observed.
2. Coexpression of ACE2 and TMPRESS2 was not detected in testis cells.
3. RNA expression of TMPRSS2 in CC was shown to be low or abscent.
4. SARS-CoV-2 infection is unlikely to have long-term effects on male and female reproductive function.

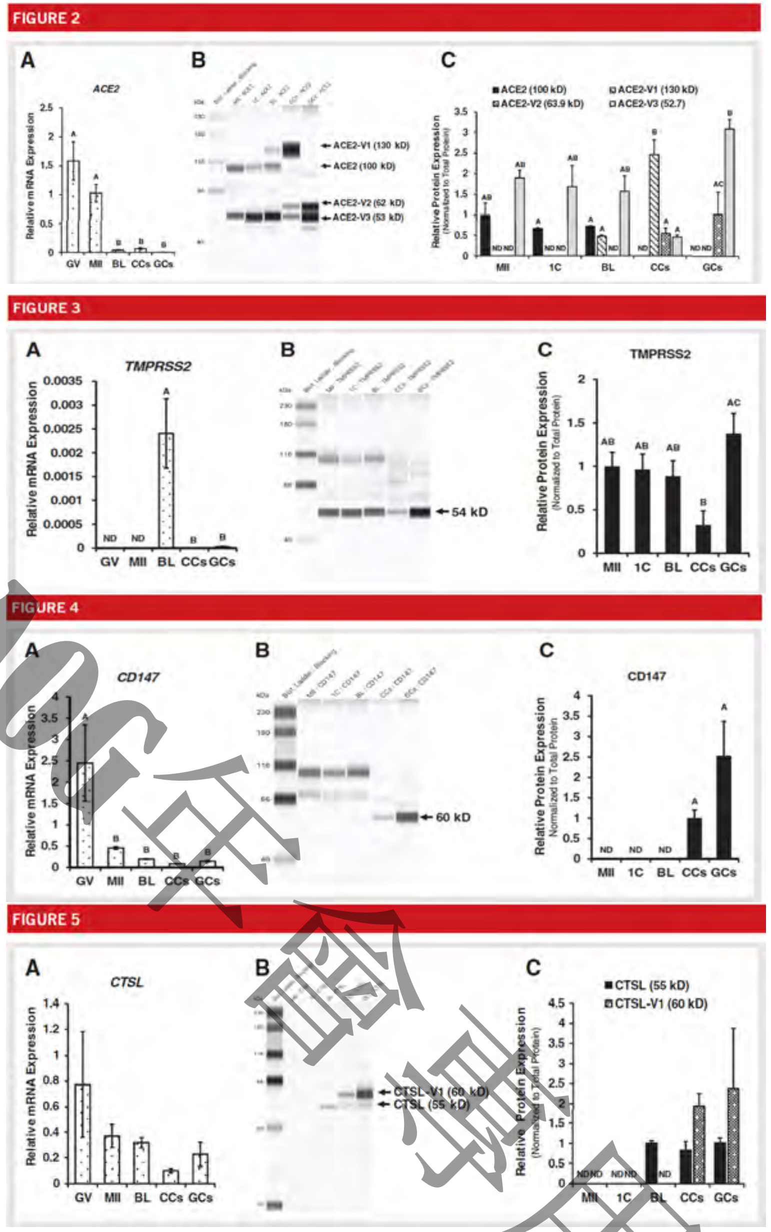
Fertil Steril® 2020;114:33-43.

Human eggs, zygotes, and embryos express the receptor angiotensin 1-converting enzyme 2 and transmembrane serine protease 2 protein necessary for severe acute respiratory syndrome coronavirus 2 infection

Sandeep K. Rajput, Ph.D.,[a] Deirdre M. Logsdon, M.S.,[a] Becca Kile, M.S.,[a] Heidi J. Engelhorn, M.S.,[a] Ben Goheen, B.S.,[a] Shaihla Khan, Ph.D.,[a] Jason Swain, Ph.D., H.C.L.D.,[a] Sue McCormick, B.S.,[a] William B. Schoolcraft, M.D.,[a] Ye Yuan, Ph.D.,[a] and Rebecca L. Krisher, Ph.D.[a,b]

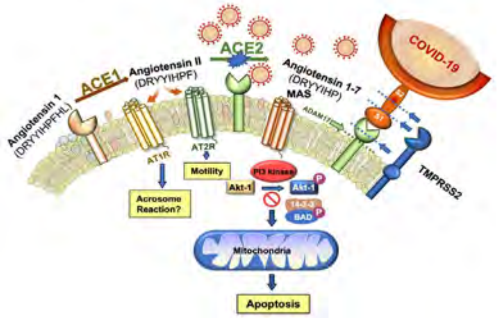
[a] Colorado Center for Reproductive Medicine, Lone Tree, Colorado, and [b] Genus PLC, DeForest, Wisconsin

Objective: To study messenger ribonucleic acid (mRNA) and protein expressions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry receptors (angiotensin 1-converting enzyme 2 [ACE2] and CD147) and proteases (transmembrane serine protease 2 [TMPRSS2] and cathepsin L [CTSL]) in human oocytes, embryos, and cumulus (CCs) and granulosa cells (GCs).
Design: Research study.
Setting: Clinical in vitro fertilization (IVF) treatment center.
Patients: Patients undergoing IVF were treated at the Colorado Center for Reproductive Medicine.
Interventions: Oocytes (germinal vesicle and metaphase II [MII]) and embryos (1-cell [1C] and blastocyst [BL]) were donated for research at the disposition by the patients undergoing IVF. Follicular cells (CC and GC) were collected from women undergoing egg retrieval after ovarian stimulation without an ovulatory trigger for in vitro maturation/IVF treatment cycles.
Main Outcome Measures: Presence or absence of ACE2, CD147, TMPRSS2, and CTSL mRNAs detected using quantitative reverse transcription polymerase chain reaction and proteins detected using capillary Western blotting in human oocytes, embryos, and ovarian follicular cells.
Results: The quantitative reverse transcription polymerase chain reaction analysis revealed high abundance of *ACE2* gene transcripts in germinal vesicle and MII oocytes than in CC, GC, and BL. ACE2 protein was present only in the MII oocytes, and 1C and BL embryos, but other ACE2 protein variants were observed in all the samples. TMPRSS2 protein was present in all the samples, whereas mRNA was observed only in the BL stage. All the samples were positive for CD147 and CTSL mRNA expressions. However, CCs and GCs were the only samples that showed coexpression of both CD147 and CTSL proteins in low abundance.
Conclusions: CCs and GCs are the least susceptible to SARS-CoV-2 infection because of lack of the required combination of receptors and proteases (ACE2/TMPRSS2 or CD147/CTSL) in high abundance. The coexpression of ACE2 and TMPRSS2 proteins in the MII oocytes, zygotes, and BLs demonstrated that these gametes and embryos have the cellular machinery required and, thus, are potentially susceptible to SARS-CoV-2 infection if exposed to the virus. However, we do not know whether the infection occurs in vivo or in vitro in an assisted reproductive technology setting yet. (Fertil Steril Sci® 2021;2:33–42. ©2021 by American Society for Reproductive Medicine.)
Key Words: SARS-CoV-2, human IVF, oocytes and embryos, ovarian cells



ACE2 mRNA: GV, MII >> CC, GC, BL
ACE2 protein: MII, 1C, BL
TMPRSS2 protein: all samples
TMPRSS2 mRNA: only BL

CD147 and CTSL mRNA: all samples
Co-expression CD147 + CTSL: CC, GC in low abundance



Rajput. SARS-CoV-2 receptors on human embryos. Fertil Steril Sci 2021.

Genomics 113 (2021) 3449–3460

Contents lists available at ScienceDirect

Genomics

journal homepage: www.elsevier.com/locate/ygeno

Co-expression of the SARS-CoV-2 entry molecules ACE2 and TMPRSS2 in human ovaries: Identification of cell types and trends with age

Meng Wu [1], Lingwei Ma [1,1], Liru Xue, Qingqing Zhu, Su Zhou, Jun Dai, Wei Yan, Jinjin Zhang *, Shixuan Wang *

Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

ARTICLE INFO

Keywords:
SARS-CoV-2
ACE2
TMPRSS2
Single-cell RNA-Seq
Ovary

ABSTRACT

The high rate of SARS-CoV-2 infection poses a serious threat to public health. Previous studies have suggested that SARS-CoV-2 can infect human ovary, the core organ of the female reproductive system. However, it remains unclear which type of ovarian cells are easily infected by SARS-CoV-2 and whether ovarian infectivity differs from puberty to menopause. In this study, public datasets containing bulk and single-cell RNA-Seq data derived from ovarian tissues were analyzed to demonstrate the mRNA expression and protein distribution of the two key entry receptors for SARS-CoV-2—angiotensin-converting enzyme 2 (ACE2) and type II transmembrane serine protease (TMPRSS2). Furthermore, an immunohistochemical study of ACE2 and TMPRSS2 in human ovaries of different ages was conducted. Differentially expressed gene (DEG) analysis of ovaries of different ages and with varying ovarian reserves was conducted to explore the potential functions of ACE2 and TMPRSS2 in the ovary. The analysis of the public datasets indicated that the co-expression of ACE2 and TMPRSS2 was observed mostly in oocytes and partially in granulosa cells. However, no marked difference was observed in *ACE2* or *TMPRSS2* expression between young and old ovaries and ovaries with low and high reserves. Correspondingly, ACE2 and TMPRSS2 were detected in the human ovarian cortex and medulla, especially in oocytes of different stages, with no observed variations in their expression level in ovaries of different ages, which was consistent with the results of bioinformatic analyses. Remarkably, DEG analysis showed that a series of viral infection-related pathways were more enriched in ACE2-positive ovarian cells than in ACE2-negative ovarian cells, suggesting that SARS-CoV-2 may potentially target specific ovarian cells and affect ovarian function. However, further fundamental and clinical research is still needed to monitor the process of SARS-CoV-2 entry into ovarian cells and the long-term effects of SARS-CoV-2 infection on the ovarian function in recovered females.

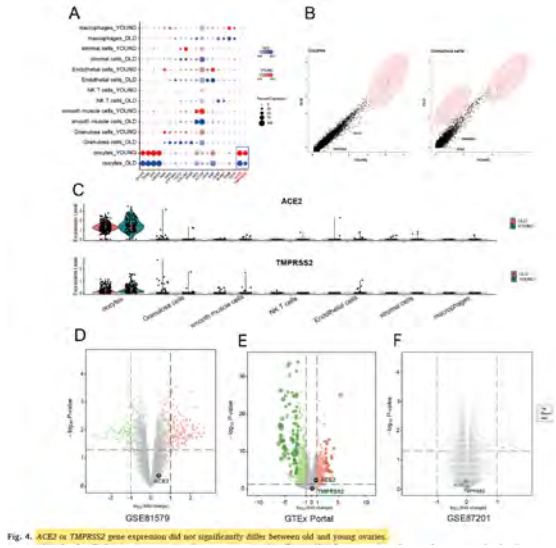


Fig. 4. *ACE2* or *TMPRSS2* gene expression did not significantly differ between old and young ovaries.

1. The co-expression of ACE2 and TMPRSS2 was observed mostly in oocytes and partially in GCs.
2. No marked difference was observed in ACE2 and TMPRESS2 expression between young and old ovaries and between low and high ovarian reserves.

Table 2
The distribution of ACE2 and TMPRSS2 in each type of ovarian cells in two scRNA-seq.

	ACE2		TMPRSS2	
	GSE130664 (%)	GSE107746 (%)	GSE130664 (%)	GSE107746 (%)
Oocytes	95.58	86.42	68.81	16.05
Granulosa cells	2.55	67.14	3.19	10.00
meiotic prophase germ cells	0.31	–	0.00	–
Stromal cells	0.58	–	0.58	–
Smooth muscle cells	2.84	–	4.26	–
Endothelial cells	2.33	–	2.33	–
Macrophages	0.70	–	0.00	–
Natural killer cells	0.00	–	0.24	–

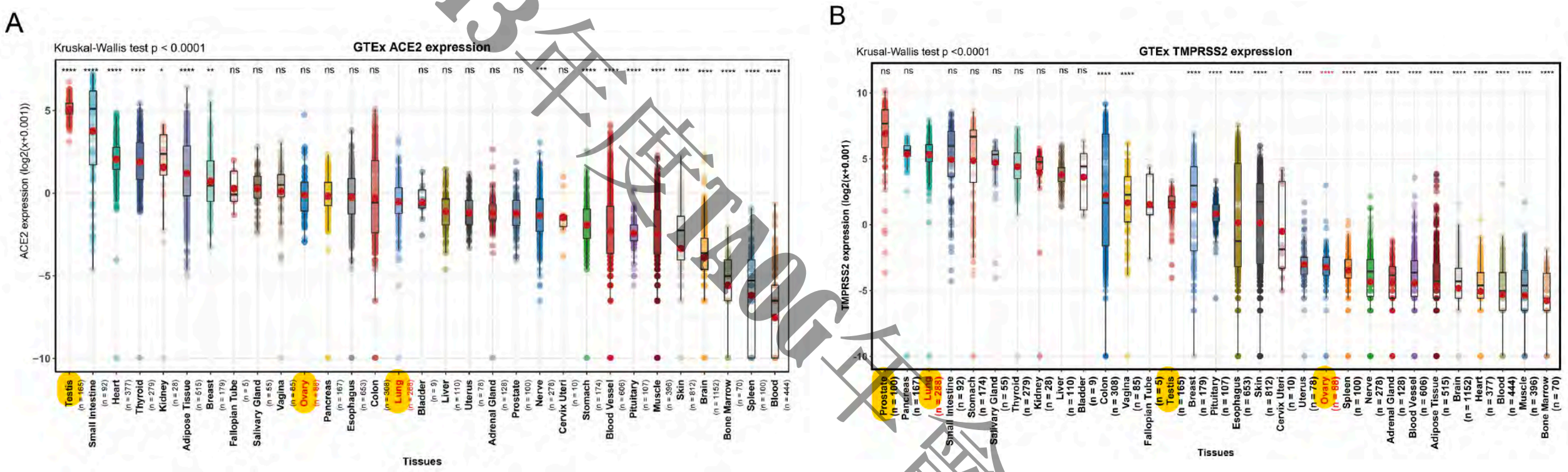


Fig. 1. mRNA expression levels of *ACE2* (A) and *TMPRSS2* (B) in multiple organs; data obtained from the Genotype-Tissue Expression (GTEx) database (a human organ database); * $p < 0.05$, ** $p < 0.001$, *** $p = 0.0001$, **** $p < 0.0001$. The vertical coordinates represent the log transformed (log2 [x + 0.001]) relative expression level of *ACE2* and *TMPRSS2*.

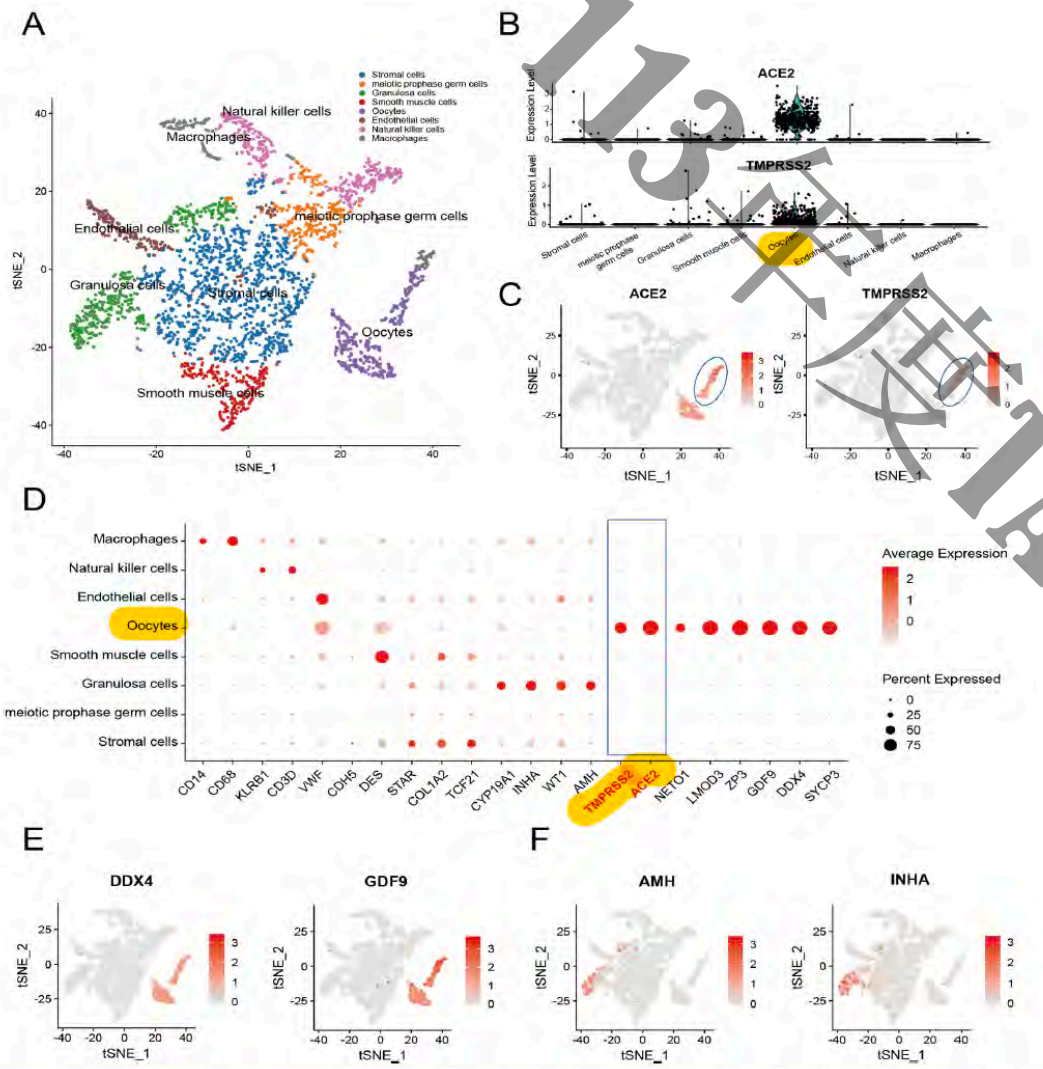


Fig. 2. Gene expression profiles of distinct ovarian cell subpopulations based on ovarian scRNA-Seq data from dataset GSE130664 (macaque ovarian single cells).

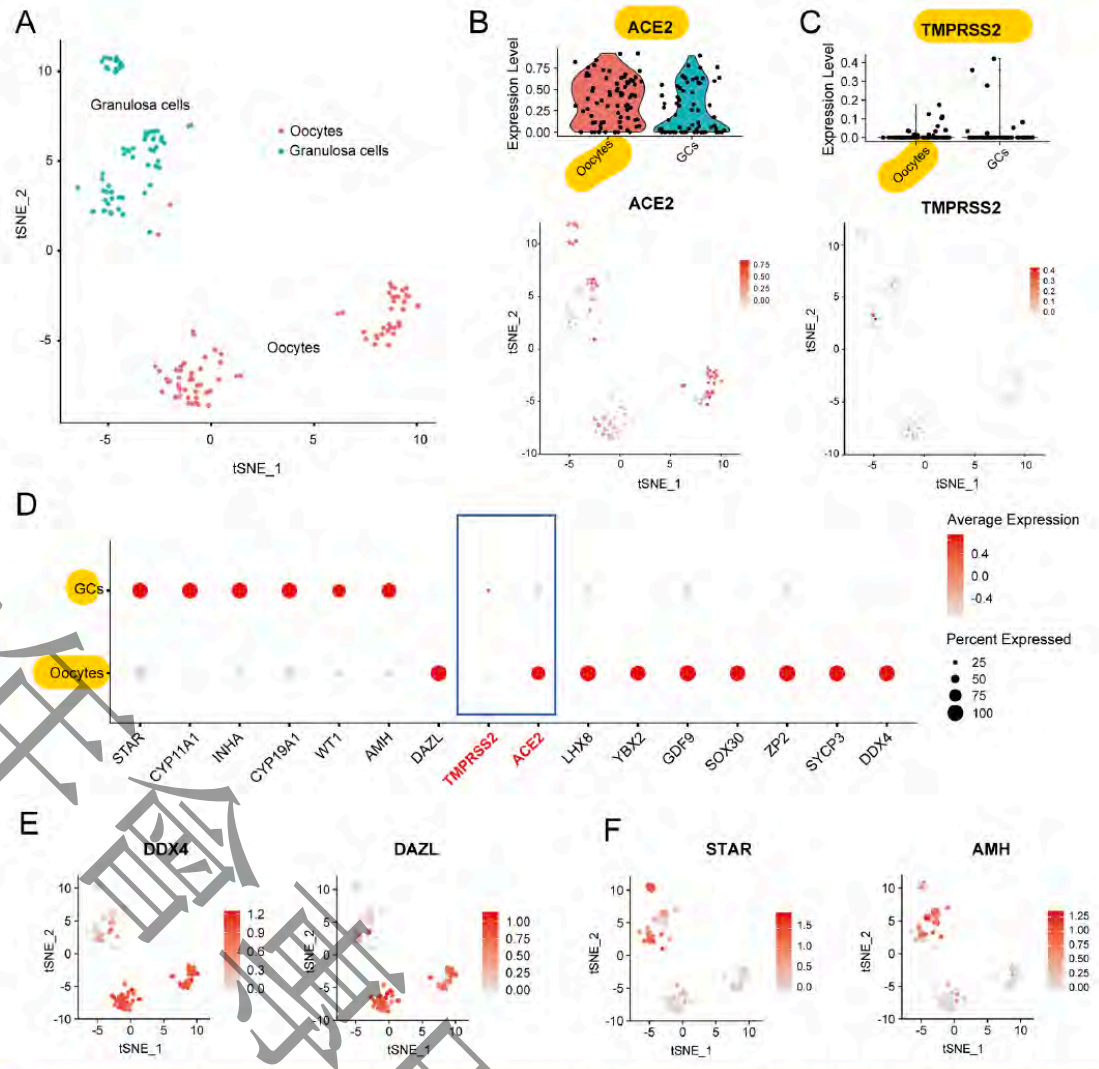
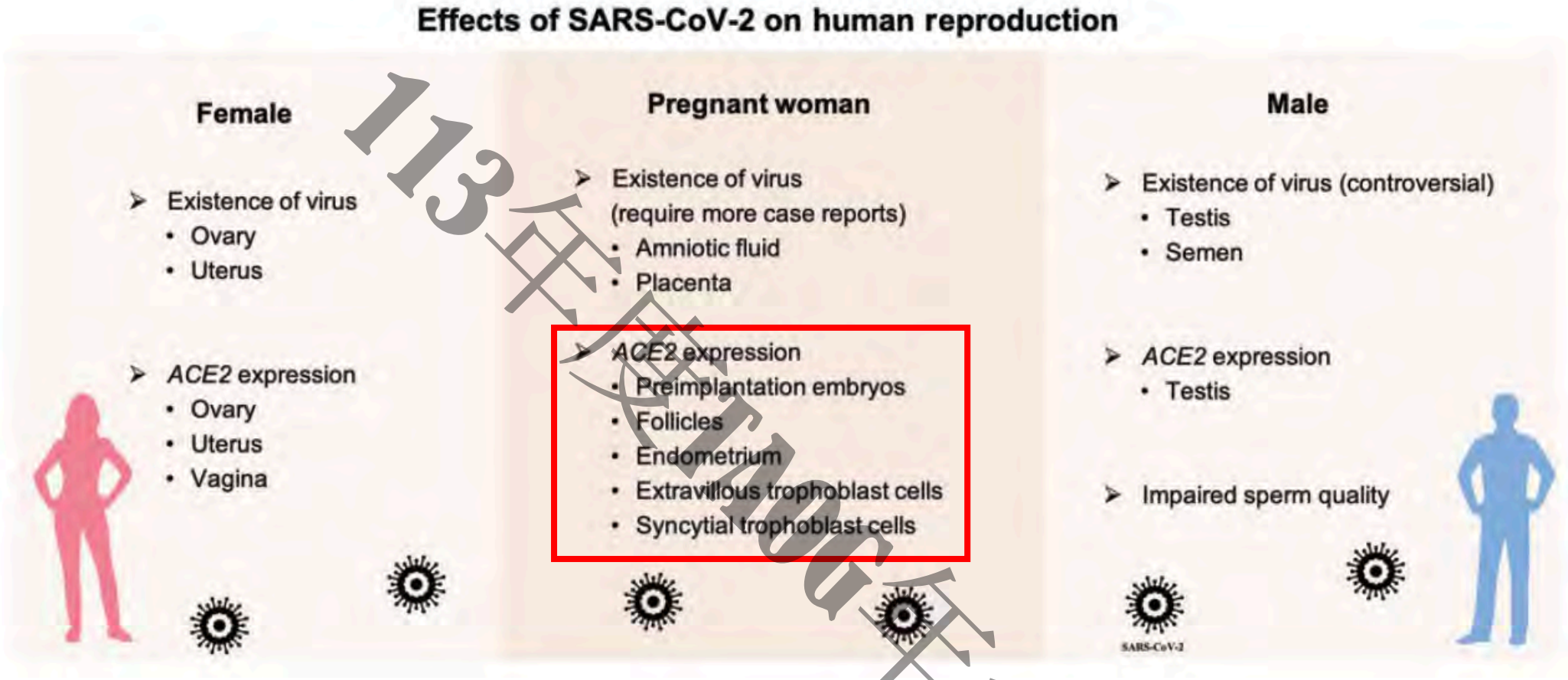
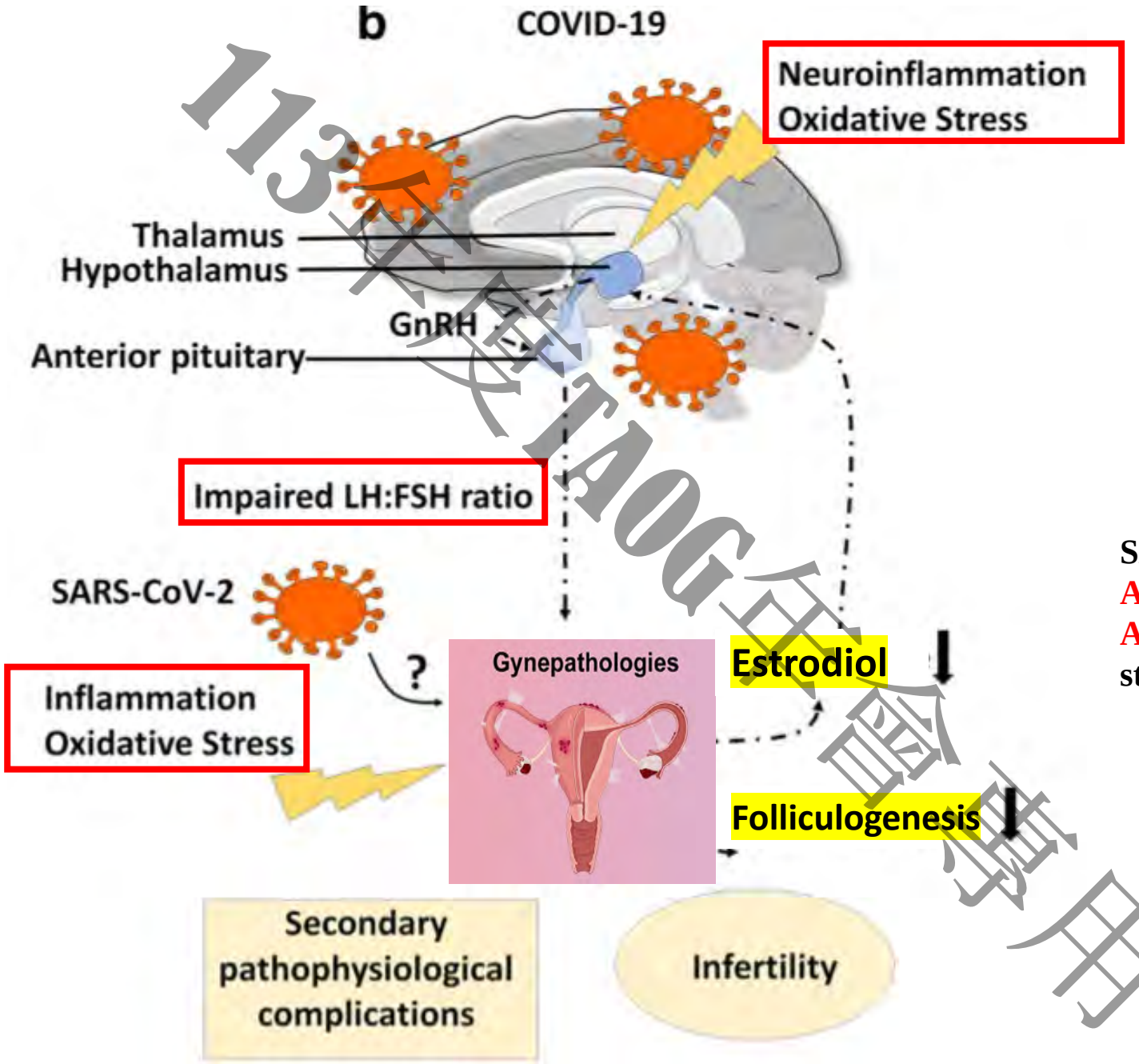


Fig. 3. Gene expression profiles of oocytes and granulosa cells based on the ovarian scRNA-Seq data from dataset GSE107746 (human oocytes and granulosa cells).



1. ACE2 is expressed in female follicles, endometrium (Algarroba et al., 2020; Hosier et al., 2020), and throughout different developmental stages of preimplantation embryos.
2. The co-expression level of ACE2 and TMPRSS2 is highest on day 6 during the embryonic development in trophectoderm (TE) cells, indicating that TE cells may be relatively susceptible to SARSCoV-2 during that time window. Thus, the potential risk of SARS-CoV-2 infection is during embryo transfer process in clinical setting.
3. ACE2 expression in endometrium may allow SARS-CoV-2 to enter endometrial epithelial and stromal cells, impairing in vivo decidualization, embryo implantation, and placentation (Chadchan et al., 2020).

Yang et al. *Journal of Molecular Cell Biology* (2021), 13(10), 695–704



SARS-CoV-2 virus downregulates ACE2, leading to increased levels of Ang II that might lead to oxidative stress and ovarian dysfunction.

Outlines

1. Introduction
2. The possible mechanisms of SARS-CoV-2 infection on female fertility
3. The clinical presentations of ovarian dysfunction during and after SARS-CoV-2 infection
4. Long COVID-19 on ovarian function and female fertility
5. COVID-19 vaccination on ovarian function and female fertility
6. Take home message

frontiers in Medicine

ORIGINAL RESEARCH
published: 19 March 2021
doi: 10.3389/fmed.2021.635255

Analysis of Ovarian Injury Associated With COVID-19 Disease in Reproductive-Aged Women in Wuhan, China: An Observational Study

Ting Ding[1], Tian Wang[1], Jinjin Zhang[1], Pengfei Cui[1], Zhe Chen[1], Su Zhou[1], Suzhen Yuan[1], Wenqing Ma[1], Minli Zhang[1], Yueguang Rong[2], Jiang Chang[3], Xiaoping Miao[3], Xiangyi Ma[1†] and Shixuan Wang[1*†]*

[1] Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetrical and Gynecological Diseases, Tongji Medical College, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China, [2] Department of Pathogen Biology, School of Basic Medicine, Huazhong University of Science and Technology, Wuhan, China, [3] Department of Epidemiology and Biostatistics, Key Laboratory for Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Sciences and Technology, Wuhan, China

Objective: This study was intended to investigate the relationship between COVID-19 disease and ovarian function in reproductive-aged women.

Methods: Female COVID-19 patients of reproductive age were recruited between January 28 and March 8, 2020 from Tongji Hospital in Wuhan. Their baseline and clinical characteristics, as well as menstrual conditions, were recorded. Differentials in ovarian reserve markers and sex hormones (including anti-Müllerian hormone [AMH], follicle-stimulating hormone [FSH], the ratio of FSH to luteinizing hormone [LH], estradiol [E2], progesterone [P], testosterone [T], and prolactin [PRL] were compared to those of healthy women who were randomly selected and individually matched for age, region, and menstrual status. Uni- and multi-variable hierarchical linear regression analyses were performed to identify risk factors associated with ovarian function in COVID-19 women.

Results: Seventy eight patients agreed to be tested for serum hormone, of whom 17 (21.79%) were diagnosed as the severe group and 39 (50%) were in the basal level group. Menstrual status ($P = 0.55$), menstrual volumes ($P = 0.066$), phase of menstrual cycle ($P = 0.58$), and dysmenorrhea history ($P = 0.12$) were similar without significant differences between non-severe and severe COVID-19 women. Significant lower serum AMH level/proportion (0.19/0.28 vs. 1.12 ng/ml, $P = 0.003/0.027$; AMH $\leq$ 1.1 ng/ml: 75/70.4 vs. 49.7%, $P = 0.009/0.004$), higher serum T (0.38/0.39 vs. 0.22 ng/ml, $P < 0.001/0.001$) and PRL (25.43/24.10 vs. 12.12 ng/ml, $P < 0.001/0.001$) levels were observed in basal level and the all-COVID-19 group compared with healthy age-matched control. When adjusted for age, menstrual status and parity variations in multivariate hierarchical linear regression analysis, COVID-19 disease was significantly associated with serum AMH ($\beta = -0.191$; 95% CI: −1.177–0.327; $P = 0.001$), T ($\beta = 0.411$; 95% CI: 11.154–22.709; $P < 0.001$), and PRL ($\beta = 0.497$; 95% CI: 10.787–20.266; $P < 0.001$), suggesting an independent risk factor for ovarian function, which accounted for 3.2% of the decline in AMH, 14.3% of the increase in T, and 20.7% of the increase in PRL.

Conclusion: Ovarian injury, including declined ovarian reserve and reproductive endocrine disorder, can be observed in women with COVID-19. More attention should be paid to their ovarian function under this pandemic, especially regarding reproductive-aged women.

Clinical Trial Number: ChiCTR2000030015.

78 patients of reproductive age

In the endometrium the expression of ACE2 is low, but it is still important for maintaining regular menstrual cycles, thus the imbalance between AngII and Ang(1–7) due to COVID-19 may lead to abnormal endometrial regeneration and proliferation and to implantation failure.

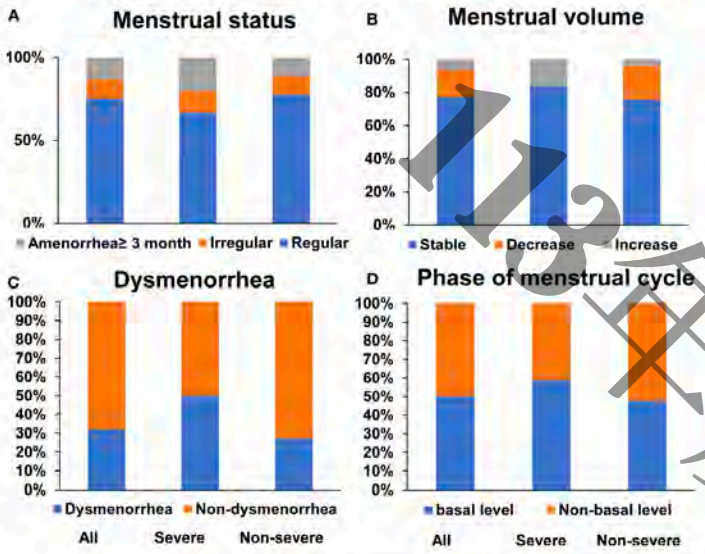


FIGURE 1 | Menstruation condition in COVID-19 reproductive-age women. Menstrual status **(A)** and menstrual volumes **(B)** in last 3 months, dysmenorrhea history **(C)** and phase of menstrual cycle **(D)** in all, severe and non-severe COVID women, respectively.

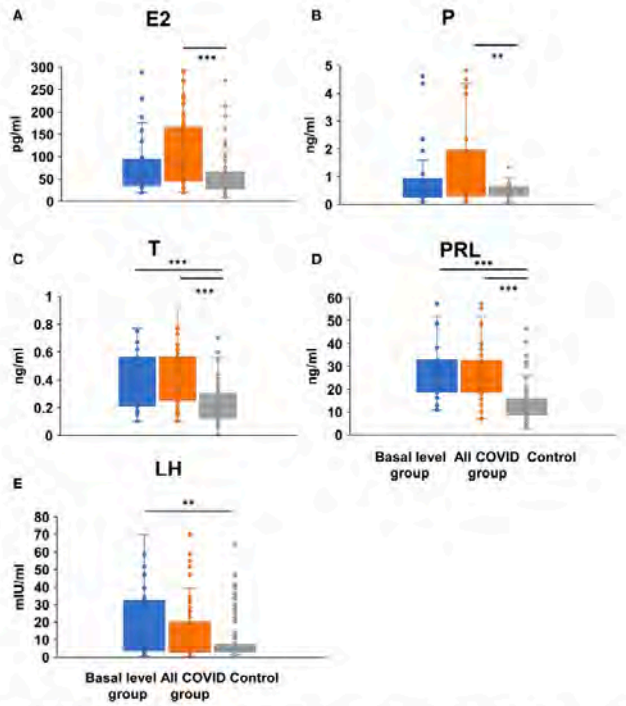


FIGURE 3 | Comparison of female sex hormones between COVID-19 patients and healthy women. Differences of serum E2 **(A)**, P **(B)**, T **(C)**, PRL **(D)**, and LH levels **(E)** were compared between basal level/all COVID-19 group and healthy control women; $^{**}P < 0.01$, $^{***}P < 0.001$.

1. Decreased levels of AMH and increased levels of T and prolactin
2. SARS-COV-2 infection was an independent risk factor for ovarian dysfunction, which accounted for 3.2% of the decline in AMH level

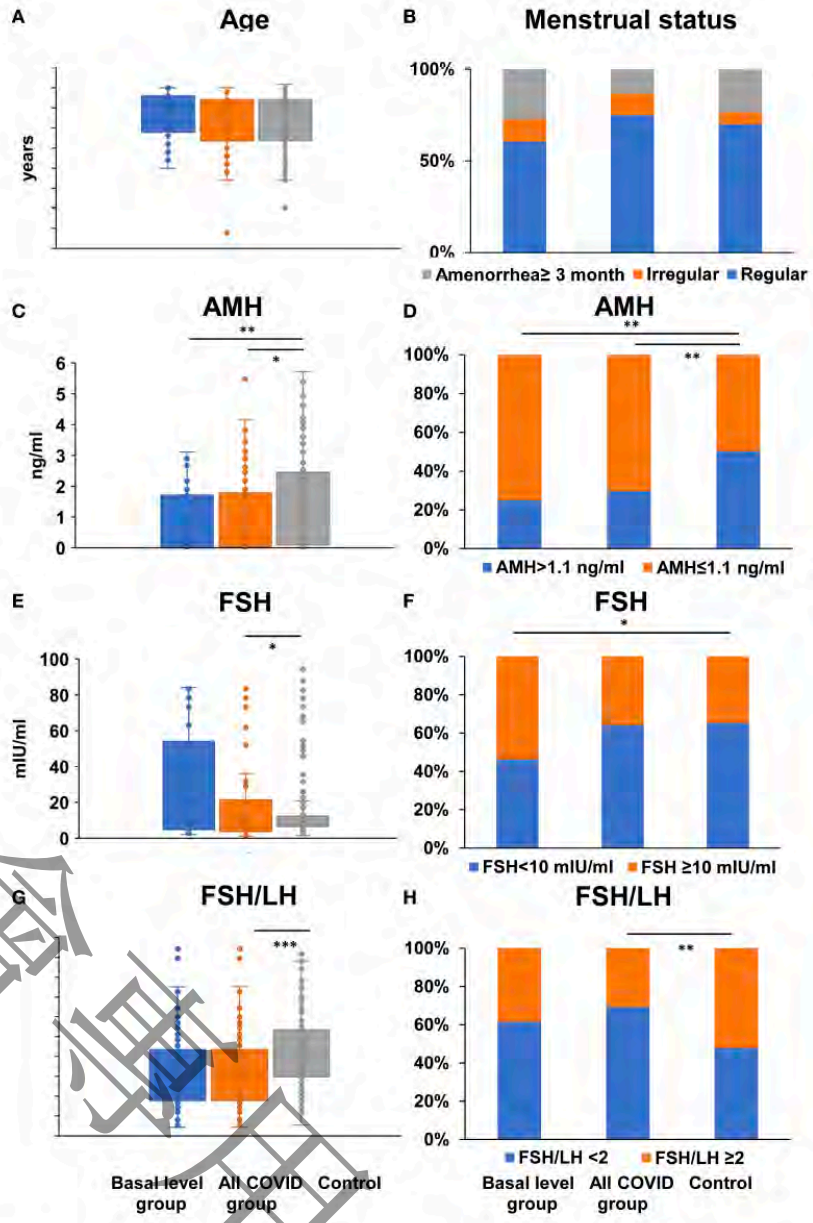


FIGURE 2 | Comparison of age, menstrual status, and ovarian reserve tests between COVID-19 patients and healthy women. Differences of age **(A)**, menstrual status **(B)**, serum AMH **(C)**, FSH level **(E)**, the ratio of FSH to LH **(G)**, the proportion of AMH ≤ 1.1 ng/ml **(D)**, FSH ≥ 10 mIU/ml **(F)**, FSH/LH ≥ 2 **(H)** were compared between basal level/all COVID-19 group and healthy control women; $^{*}P < 0.05$ $^{**}P < 0.01$ $^{***}P < 0.001$.

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/radcr

Case Report

Ovarian vein thrombosis as a first manifestation of COVID-19 infection ☆

*Noor Badrawi, MD, Shareefa Abdulghaffar, MD**

Department of Radiology, Rashid Hospital, Dubai Health Authority, PO Box 4545, Dubai, United Arab Emirates

ARTICLE INFO

Article history:
Received 5 August 2021
Accepted 11 August 2021
Available online 16 August 2021

Keywords:
Ovarian vein thrombosis
Novel coronavirus
COVID-19
SARS-CoV-2
Computed tomography

ABSTRACT

Coronavirus disease 2019 (COVID-19) infection is associated with high risk of venous thromboembolic events mainly pulmonary embolism or deep venous thrombosis of the lower limbs. Ovarian vein thrombosis is a rare and serious condition usually seen in the immediate postpartum period and other conditions including pelvic inflammatory diseases, gynecological malignancies, hypercoagulable states, and few cases to date have reported ovarian vein thrombosis as a complication of COVID-19 infection. Patient with ovarian vein thrombosis usually presents with fever and lower abdominal pain that can mimic acute surgical abdomen and high index of suspicion is required for diagnosis. We report a case of a 41-year-old Asian female presented to our hospital with fever and acute lower abdominal pain. Laboratory findings show positive COVID-19 test and high D-dimer. Patient underwent computed tomography of the abdomen and pelvis and a confirmed diagnosis of right ovarian vein thrombosis was made. Patient was treated with anticoagulation and empirical antibiotics and her symptoms have significantly improved.

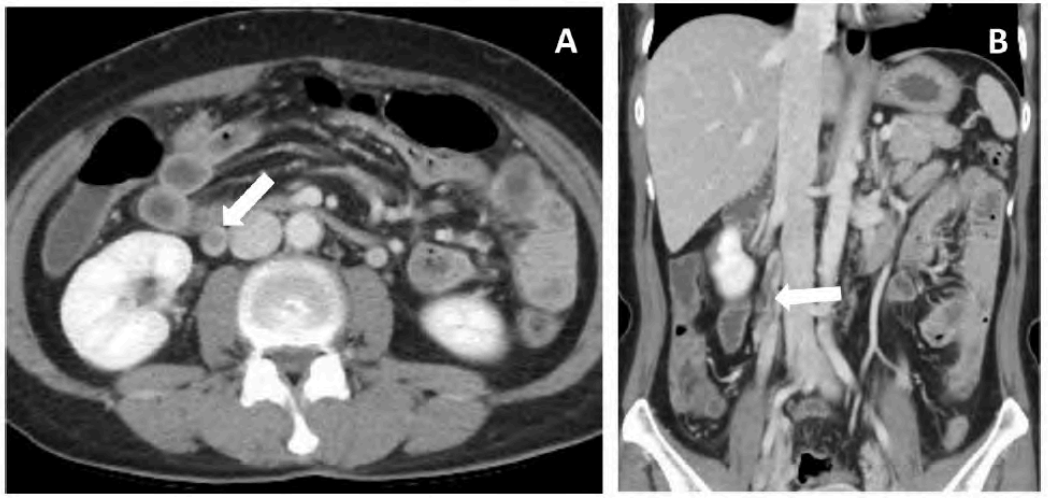


Fig. 1 – Axial (A) and coronal (B) intravenous contrast-enhanced computed tomography images of the abdomen and pelvis showing thrombosis of the right ovarian vein (white arrow).

90% OVT at Rt ovary.
Fever, low abdominal pain
High D-Dimer
=> predisposing to pulmonary emboli, ovarian abscesses, ovarian infarctions, septic thrombophlebitis, uterine necrosis or uteteral compression.
=> poor ovarian function

CASE REPORT

COVID-19-related premature ovarian insufficiency: case report and literature review

K. Pankiewicz[a], E. Chotkowska[a], B. Nowakowska[b], M. Gos[b] and T. Issat[a]

[a]Department of Obstetrics and Gynecology, Institute of Mother and Child, Warsaw, Poland; [b]Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland

ABSTRACT

Objective: The aim of this study is to present the case report of a 36-year-old woman developing premature ovarian insufficiency (POI) after COVID-19 and review the literature referring to the possible impact of SARS-CoV-2 infection on female reproduction.

Methods: A 36-year-old nulligravida with normal menstrual cycles, non-smoker, with a normal body mass index and no pelvic surgery or oncological treatment in her medical history presented to the Infertility Center of the Institute of Mother and Child in Warsaw after a year of unsuccessful attempts to get pregnant. During diagnostic process she was affected by COVID-19 with a mild manifestation and thereafter she presented amenorrhea with intense hot flushes. Further diagnostic confirmed the diagnosis of POI.

Results: There is a strong molecular basis for a possible effect of SARS-CoV-2 infection on the female reproductive system; however, the results of available research are conflicting. All of these aspects are discussed in detail.

Conclusions: SARS-CoV-2 infection may cause serious complications that cast a long shadow on a patient's future life and health. Further research is needed to assess the real impact of SARS-CoV-2 infection on female reproductive health, as well as potential preventive and therapeutic strategies for women affected with COVID-19.

ARTICLE HISTORY
Received 3 January 2023
Revised 15 June 2023
Accepted 3 August 2023
Published online 31 August 2023

KEYWORDS
Premature ovarian insufficiency; COVID-19; infertility; ovarian dysfunction; reproductive health

Before COVID-19
Cycle: 28-32 d

Mild S/S of COVID-19
Fever, cough, myalgia

5 months after COVID-19
Amenorrhea
Hot flushes
FSH:44.2 IU/l
E2:167.62 pg/ml
P4: 2.23 ng/ml
Prolactin: 287 mIU/l (within normal range)
TSH:0.744 mIU/l
Testosterone: 0.34 nmol/l
Gyn U/S: no follicles
POI was diagnosed

7 months after COVID-19
FSH: 129.5IU/l
AMH: 0.13 ng/ml
Karyotype: 46, XX
FMR1 gene: no mutation

RX: HRT

CLIMACTERIC
2023, VOL. 26, NO. 6, 601–604
https://doi.org/10.1080/13697137.2023.2246878

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

Autoimmune oophoritis

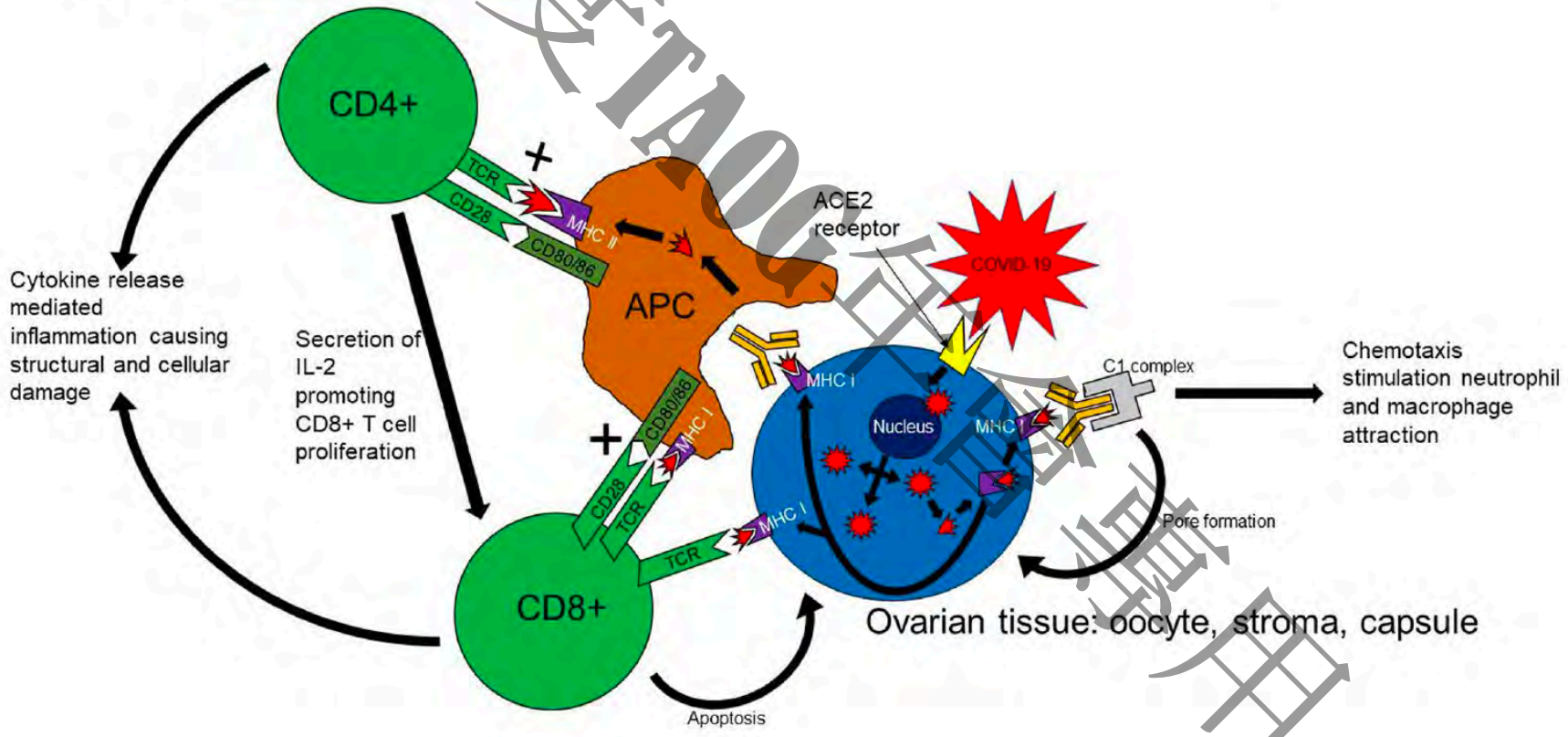


FIGURE 1 Possible mechanism of COVID-19 induced premature ovarian insufficiency

Cureus

Open Access Case Report

DOI: 10.7759/cureus.37379

Transient Premature Ovarian Insufficiency Post-COVID-19 Infection

Colleen N. Gorman [1], Tori E. Abdalla [2], Yasmina Sultan [3], Spencer A. Grabois [4], Ellen G. Wood [5]

1. Obstetrics and Gynecology, Nova Southeastern University Dr. Kiran C. Patel College of Osteopathic Medicine, Davie, USA 2. Medicine, Philadelphia College of Osteopathic Medicine, Philadelphia, USA 3. Biomedical Sciences Program, Philadelphia College of Osteopathic Medicine, Philadelphia, USA 4. Obstetrics and Gynecology, Mount Sinai Medical Center, Miami, USA 5. Reproductive Endocrinology and Infertility, IVFMD South Florida Institute for Reproductive Medicine, Cooper City, USA

Corresponding author: Colleen N. Gorman, cngorman0209@gmail.com

Review began 04/02/2023
Review ended 04/04/2023
Published 04/10/2023

Abstract

Anti-ovarian antibodies (AOAs) have been linked to autoimmune premature ovarian insufficiency (POI). This report details a case in which a patient experienced transient POI after a COVID-19 infection and tested positive for AOA. After treatment with oral contraceptives and subsequent high-dose oral corticosteroids, the patient underwent fertility treatment with in vitro fertilization (IVF). A total of 23 oocytes were retrieved. Two euploid blastocysts and three untested blastocysts were successfully created. This report hypothesizes the connection between autoimmune POI, AOA, and COVID-19. Conflicting data have been reported linking COVID-19 and ovarian injury. However, it is suggested that COVID-19 transiently impacts the menstrual cycle and anti-Mullerian hormone (AMH) levels. Treatment to overcome poor ovarian response due to AOA has not been adequately determined; however, similar autoimmune conditions have been successfully treated with corticosteroids.

Conclusions

This is a case of transient autoimmune oophoritis resulting in POI after infection with COVID-19, which was successfully treated with corticosteroids. Evaluation of infertility patients with self-report of recent infections should include screening for AOA as a cause of infertility. Early detection of AOA in patients with no other identifiable causes of infertility can decrease the time to clinical pregnancy with cost-effective medication. Management of patients with a positive AOA screening test includes treatment with corticosteroids before and during ovarian stimulation. Evaluating patient titers during stimulation, before and after embryo transfer, and throughout the resulting pregnancy for medication management can be considered.

1. A case of transient autoimmune oophoritis resulting in POI after COVID-19
2. Screening: anti-ovarian Ab (AOA)
3. Treatment with corticosteroids before and during ovarian stimulation.
4. Evaluating AOA titers during ovarian stimulation, before and after ET, and during pregnancy

2023 Gorman et al. Cureus 15(4): e37379. DOI 10.7759/cureus.37379

BBA - Molecular Basis of Disease 1868 (2022) 166295

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

SARS-CoV-2 infection negatively affects ovarian function in ART patients

Yamila Herrero [a], Natalia Pascuali [a], Candela Velázquez [a], Gonzalo Oubiña [a], Vanesa Hauk [b], Ignacio de Zúñiga [c], Mariana Gómez Peña [c], Gustavo Martínez [d], Mariano Lavolpe [e], Florencia Veiga [f], Fernando Neuspiller [f], Dalhia Abramovich [a], Leopoldina Scotti [a,g], Fernanda Parborell [a,*]

[a] Ovarian Pathophysiology Studies Laboratory, Institute of Experimental Biology and Medicine (IByME) – CONICET, Buenos Aires, Argentina
[b] Immunopharmacology Laboratory, Institute of Biological Chemistry (IQUIBICEN), School of Exact and Natural Sciences, University of Buenos Aires-CONICET, Buenos Aires, Argentina
[c] Pregna Medicina Reproductiva, Buenos Aires, Argentina
[d] Medicina Reproductiva Fertilis, Buenos Aires, Argentina
[e] In Vitro Buenos Aires, Buenos Aires, Argentina
[f] IVI, Buenos Aires, Argentina
[g] Centro de Investigaciones y Transferencia del Noroeste de la Provincia de Buenos Aires (CITNOBA) – CONICET - UNNOBA – UNSAdA, San Antonio de Areco, Argentina.

ABSTRACT

Several organs, such as the heart, breasts, intestine, testes, and ovaries, have been reported to be target tissues of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. To date, no studies have demonstrated SARS-CoV-2 infection in the female reproductive system. In the present study, we investigated the effects of SARS-CoV-2 infection on ovarian function by comparing follicular fluid (FF) from control and recovered coronavirus disease 2019 (COVID-19) patients and by evaluating the influence of these FF on human endothelial and non-luteinized granulosa cell cultures. Our results showed that most FFs (91.3%) from screened post COVID-19 patients were positive for IgG antibodies against SARS-CoV-2. Additionally, patients with higher levels of IgG against SARS-CoV-2 had lower numbers of retrieved oocytes. While VEGF and IL-1β were significantly lower in post COVID-19 FF, IL-10 did not differ from that in control FF. Moreover, in COV434 cells stimulated with FF from post COVID-19 patients, steroidogenic acute regulatory protein (StAR), estrogen-receptor β (Erβ), and vascular endothelial growth factor (VEGF) expression were significantly decreased, whereas estrogen-receptor α (ERα) and 3β-hydroxysteroid dehydrogenase (3β-HSD) did not change. In endothelial cells stimulated with post COVID-19 FF, we observed a decrease in cell migration without changes in protein expression of certain angiogenic factors. Both cell types showed a significantly higher γH2AX expression when exposed to post COVID-19 FF. In conclusion, our results describe for the first time that the SARS-CoV-2 infection adversely affects the follicular microenvironment, thus dysregulating ovarian function.

- 80 women (21-41y) undergoing ART procedure between Nov 2020 and April 2021
- Control (n=34), post COVID-19 patients (n=46)(mild symptoms)(PCR diagnosed)
- Time interval between the infection and retrieval of FF: 2-9 months (average: 4.5 months)
- FF was extracted from 16-20 mm follicle size. No flush and only macroscopically clear fluid was collected.

Table 1
Clinical information of control patients and post COVID-19 patients.

Baseline characteristics of patients	Control patients (n = 34)			Recovered COVID-19 patients (n = 46)			P value
	Mean	Min–Max	SEM	Mean	Min–Max	SEM	
Age (years)	33.09	23–38	0.60	33.43	21–44	1.02	n.s.
Number of oocytes retrieved in patients < 35 years	11.84	8–23	0.85	13.80	0–30	2.21	n.s.
Number of oocytes retrieved in patients > 35 years	11.11	6–16	0.95	6.95	0–15	0.95	0.0187
MII oocytes (n, %)	9.03 (79.84%)	6–16	0.61	11.98 (82.23%)	0–30	1.41	n.s.
Basal serum estradiol (pg/ml)	33.00	19–46	7.81	42.70	25–56	3.45	n.s.
Serum estradiol on trigger day (pg/ml)	2710	400–5772	576.9	1424	325–3728	1152	n.s.
Basal serum progesterone (ng/ml)	1.09	0.52–1.86	0.18	1.37	0.30–4.38	0.58	n.s.
Basal serum prolactin (ng/ml)	20.37	6.20–48	3.01	15.74	1–36.20	1.83	n.s.
AMH (ng/ml)	2.067	0.5–4.4	0.32	2.917	0.31–5.7	0.48	n.s
Antral follicles count (AFC)	12.64	7–20	0.77	12.50	4–22	0.99	n.s
BMI	23.43	18.70–31	0.98	23.01	18–29.36	0.55	n.s
Time from COVID-19 infection (months)	–	–	–	4.5	2–9	0.37	–

Data are expressed as the mean ± standard error of the mean. Student's *t*-test was used for comparisons between groups. Statistical significance was defined as <0.05.

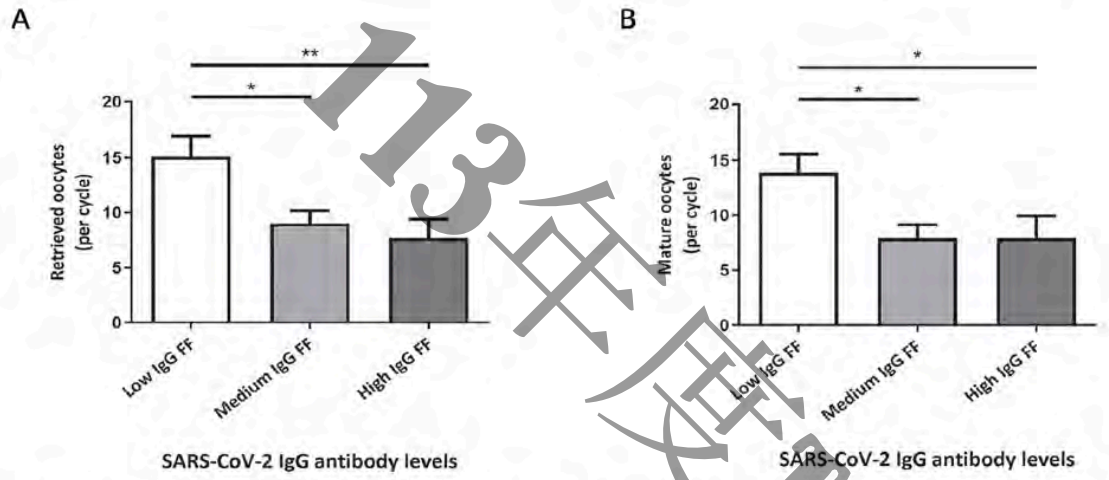


Fig. 1. Retrieved and mature oocytes from patients with low-, medium- and high-level SARS-CoV-2 IgG antibodies in FF. (A) The number of retrieved oocytes was significantly lower in the post COVID-19 subgroups as levels of SARS-CoV-2 IgG were higher (low vs. medium, $*p < 0.05$; low vs. high, $**p < 0.01$). (B) Similar results were obtained for the number of mature oocytes (low vs. medium and high, $*p < 0.05$).

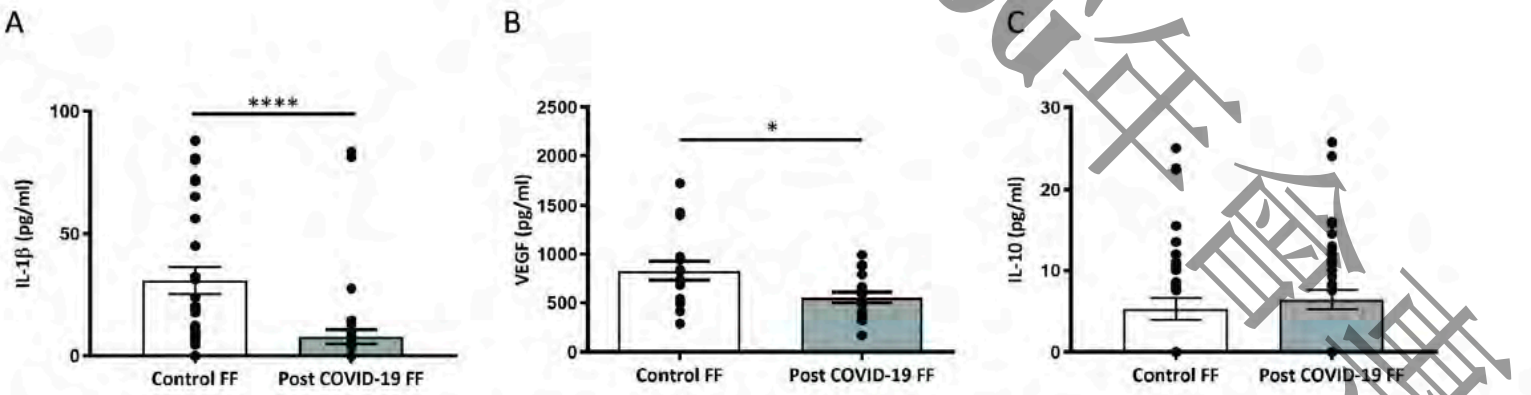


Fig. 2. VEGF, IL-1β and IL-10 concentration in control and post COVID-19 FF determined by ELISA. IL-1β (A) and VEGF(B) concentrations were decreased in FF from post COVID-19 compared with that in FF from control patients (VEGF: $*p < 0.05$, IL-1β: $****p < 0.0001$). No differences were found between groups in terms of IL-10 levels (C) ($p = 0.4$).

1. Both in women recovered from COVID-19 and in vaccinated women anti-SARS-CoV-2 IgG antibodies are present in FF.
2. VEGF, IL-1β decreased in post COVID-19 FF.
3. No differences between groups in terms of IL-10 level

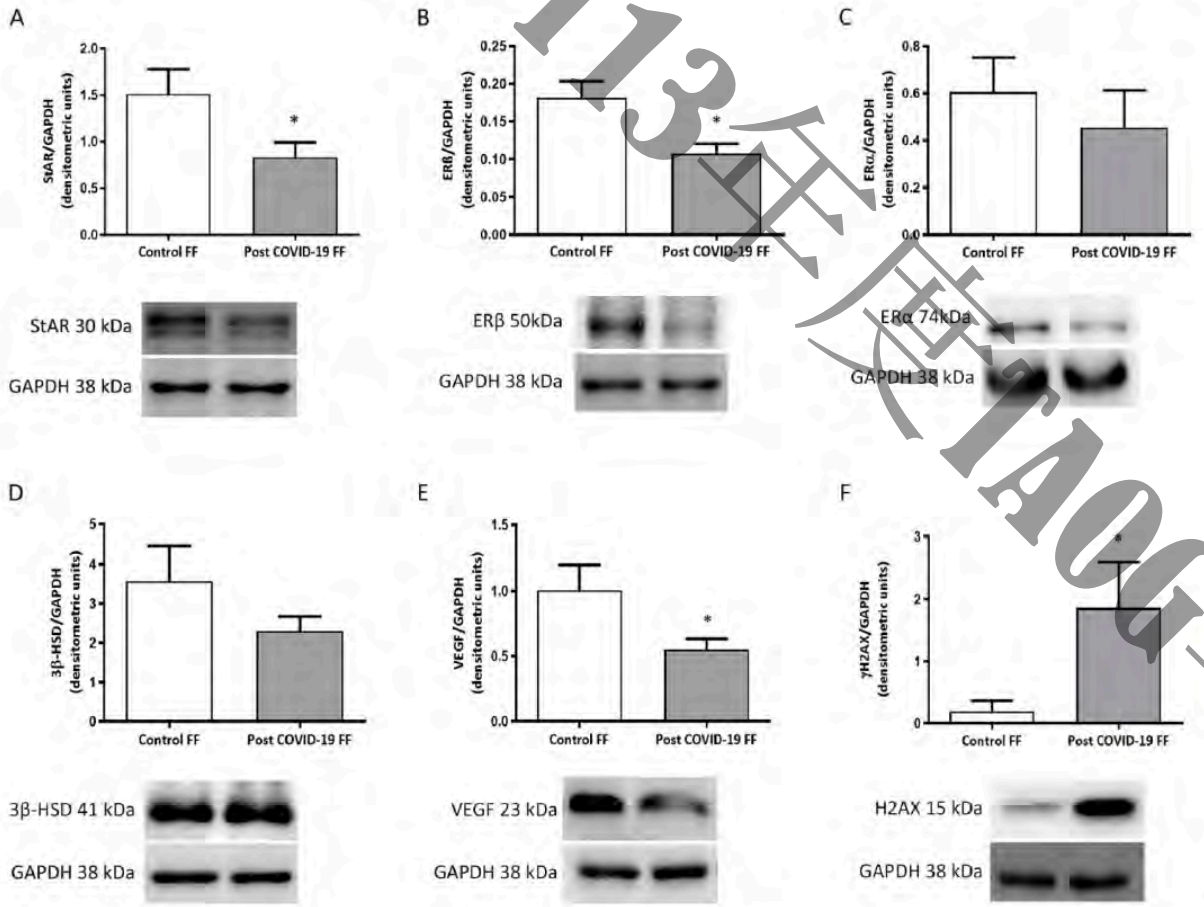


Fig. 3. Effect of FF from post COVID-19 patients on protein expression in granulosa cells. The following proteins were measured by Western Blot: StAR (A); ERβ (B); ERα (C); 3β-HSD (D); VEGF (E); γH2AX (F). Densitometric quantification showed decreased levels of StAR (A; $p < 0.05$) and ERβ (B; $p < 0.05$) in cells stimulated with post COVID-19 FF, whereas protein levels of ERα (C) and 3β-HSD (D) remained unchanged between both groups. VEGF levels were significantly lower ($p < 0.05$) in COV434 cells incubated with FF from post COVID-19 patients compared with those incubated with control FF (E). Ovarian cells stimulated with FF from post COVID-19 patients expressed higher levels of γH2AX than cells stimulated with control FF (F; $p < 0.05$). In all cases, representative immunoblots are shown in the lower panels. Data are expressed as means ± SEM normalized to GAPDH. Results were obtained from three independent experiments. * $p < 0.05$.

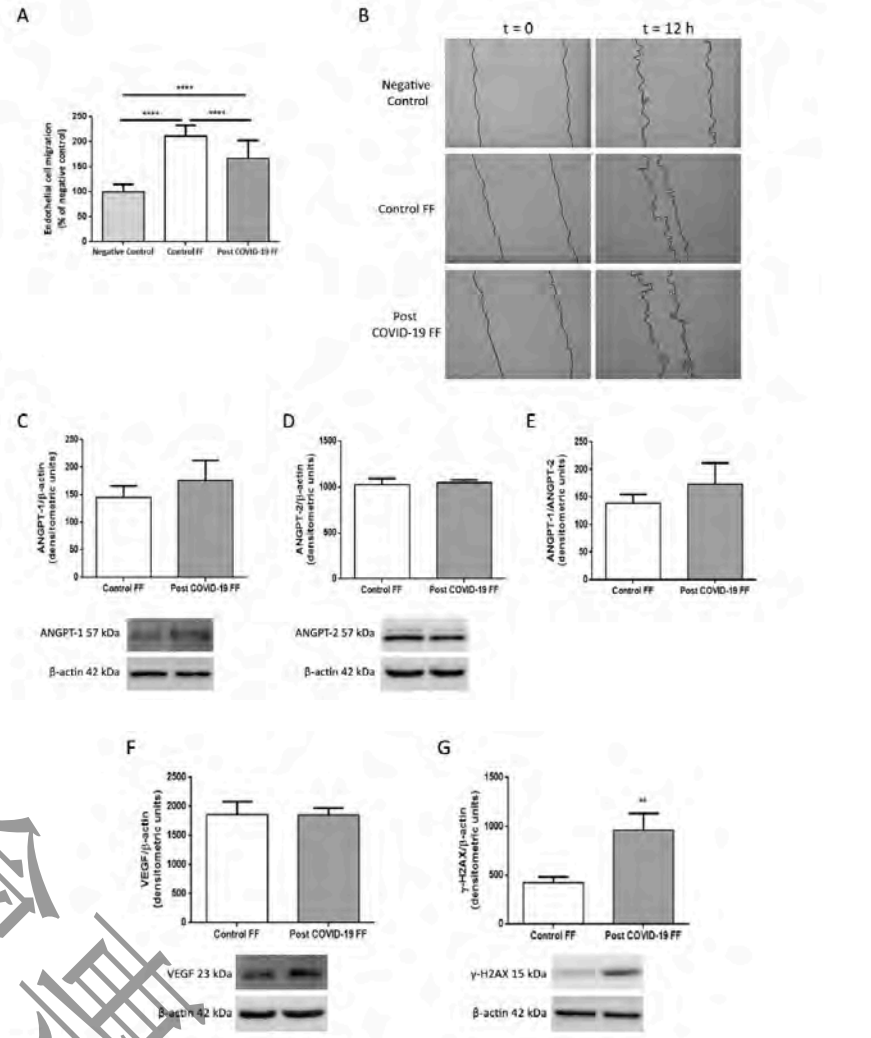


Fig. 4. Effects of FF from recovered COVID-19 patients on endothelial cells
Endothelial migration of EA.hy926 cells stimulated with control or post COVID-19 FF.
(A) Quantification of the wound-healing assay. The columns show the percentage of endothelial cell migration normalized to the negative control, which is presented as 100%. Data are expressed as means ± SEM. (B) Representative images taken immediately after wound scratching (t 0) and after 12 h (t 12). Black lines represent the migration fronts. Effects of stimulation with control or post COVID-19 FF on the expression of ANGPT-1 (G); ANGPT-2 (D); ANGPT-1/ANGPT-2 (E); VEGF (F) and γH2AX (G) in EA.hy926 cells. The graphs show the densitometric analysis of protein levels. The density of each band was normalized to the density of the β-actin bands. Lower panels show representative blots for each protein analyzed. * $p < 0.05$.

The results of available clinical studies concerning ovarian function after COVID-19 are conflicting

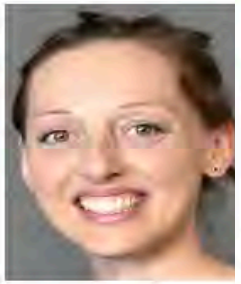
Not affect

- Kolanska et al. investigated 118 women ART procedures, including 14 (11.9%) COVID-19 positive patients, and concluded that there were no differences between the groups in baseline AMH and in AMH during ART treatment levels, as well as in the difference between these two AMH concentrations (Reprod Biomed Online. 2021;43(6):1117–1121.)
- Li et al. compared 237 COVID-19 positive women with age-matched healthy controls and found no differences in FSH, LH, E2, P4 and T and AMH levels between the groups. There was also no difference in studied parameters between patients with mild and severe SARS-CoV-2 infection. (Reprod Biomed Online. 2021;42(1):260–267)
- Madendag et al. performed a study including 132 women with unexplained infertility and compared their FSH, LH, E2 and AMH concentrations before and after COVID-19. They found no significant differences in all studied hormones (Reprod Biomed Online. 2022;45(1):153–158.)

RB

ARTICLE

Mild C
ovariar



KEY MESSAGE
Mild COVID-19 i
tested during the
between groups

TABLE 1 CHARACTERISTICS OF THE STUDY POPULATIONS

	COVID RDT positive(n = 14)	COVID RDT negative(n = 104)	P-Value
Age, years, mean (SD)	35.7 (4.2)	34.5 (4.5)	0.32
BMI, kg/m^2, mean (SD)	23.1 (3.7)	24.3 (5.5)	0.29
Tobacco smoking, n (%)	2 (14)	18 (17)	0.78
IOP, n (%)	1 (7)	22 (21)	0.21
Endometriosis, n (%)	3 (21)	30 (29)	0.56
Fallopian tube pathology, n (%)	4 (29)	14 (13)	0.14
Initial AMH concentration, ng/ml, median (IQR)	2.87 (1.69–3.99)	1.76 (0.88–3.00)	0.13
Period between the two AMH tests, days, median (IQR)	254 (211–285)	268 (158–327)	0.77
Art protocol			0.38
IVF/ICSI, n (%)	11 (79)	64 (62)	
Fertility preservation, n (%)	0 (0)	17 (16)	
Artificial insemination, n (%)	2 (14)	18 (17)	
Embryo transfer, n (%)	1 (7)	5 (5)	
Oestrogen concentration on AMH testing day, ng/ml, median, IQR	718 (239–1534)	664 (277–1353)	0.87

AMH, anti-Müllerian hormone; ART, assisted reproductive technology; BMI, body mass index; IOP, insufficient ovarian reserve; IQR, interquartile range; IVF/ICSI, IVF and intracytoplasmic sperm injection; RDT, rapid diagnostic test.

TABLE 2 ANTI-MÜLLERIAN HORMONE CONCENTRATIONS IN COVID RAPID DIAGNOSTIC TEST POSITIVE AND COVID RAPID DIAGNOSTIC TEST NEGATIVE GROUPS

	COVID RDT positive (n = 14)	COVID RDT negative (n = 104)	P-value
New AMH concentration, ng/ml, median (IQR)	1.51 (0.82–2.38)	1.00 (0.49–1.99)	0.27
Change in AMH, ng/ml, median (IQR)	–1.33 (–0.35 to –1.61)	–0.59 (–0.15 to –1.11)	0.22

RBMO

ELSEVIER

ARTICLE

COVID-19 disease does not cause ovarian injury in women of reproductive age: an observational before-and-after COVID-19 study

BIOGRAPHY

Dr Ilknur Col Madendag is a Gynaecologist at the Department of Obstetrics and Gynecology, Health Sciences University, Kayseri Medical Faculty City Hospital, Turkey. Her research focuses on ovarian endocrinology and infertility.

Ilknur Col Madendag[1,*], Yusuf Madendag[2], Ayse Turunc Ozdemir[3]

KEY MESSAGE

Ovarian reserve of women before COVID-19 disease was compared with ovarian reserve of the same women after COVID-19 disease. This was a unique cohort, which included women within a narrow age range with two AMH measurements pre- and post-COVID. The SARS-CoV-2 virus does not impact on ovarian reserve.

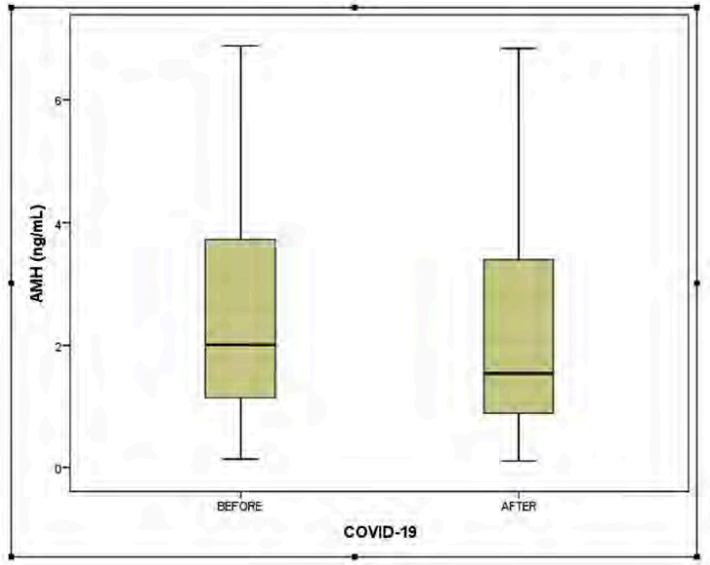


TABLE 2 COMPARISON OF THE REPRODUCTIVE FUNCTION BETWEEN GROUPS

	Before COVID-19 disease	After COVID-19 disease	*P*-value
Menstrual volume changes last 3 months			
Decrease in menstrual volume	10/132 (7.6)	21/132 (15.9)	0.035[a]
Increase in menstrual volume	12/132 (9.1)	16/132 (12.1)	0.215[a]
Irregular menstrual cycle	12/132 (9.1)	21/132 (15.9)	0.094[a]
AMH (ng/ml)	2.01 (1.09–3.78)	1.74 (0.88–3.41)	0.097[b]
Log(AMH)	0.481 ± 0.238	0.435 ± 241	0.118[b]
FSH (mIU/ml)	4.91 (1.99–8.58)	5.41 (2.29–8.99)	0.118[b]
LH (mIU/ml)	4.14 (2.08–7.07)	4.72 (1.90–8.11)	0.201[b]
Oestradiol (ng/ml)	55.42 (25.21–79.14)	58.86 (28.61–78.90)	0.181[b]
FSH/LH	1.42 (0.96–1.88)	1.61 (0.89–1.92)	0.268[b]

International Journal of
Environmental Research and Public Health

MDPI

Review

The Effects of SARS-CoV-2 Infection on Female Fertility: A Review of the Literature

Andreea Carp-Veliscu [1,2], Claudia Mehedintu [1,3,*], Francesca Frincu [1,3], Elvira Bratila [1,2], Simona Rasu [2], Ioana Iordache [1,2], Alina Bordea [1,2] and Mihaela Braga [2]

1 Department of Obstetrics and Gynecology, Carol Davila University of Medicine and Pharmacy, 020021 Bucharest, Romania; andreea_veliscu@yahoo.com (A.C.-V.); francesca.frincu@drd.umfcd.ro (F.F.); elvira.bratila@umfcd.ro (E.B.); ioana.iordache@drd.umfcd.ro (I.I.); alinaelenabordea@yahoo.com (A.B.)
2 Panait Sarbu Clinical Hospital of Obstetrics and Gynaecology, 060251 Bucharest, Romania; simona.rasu8@gmail.com (S.R.); drmihaelabraga@gmail.com (M.B.)
3 Nicolae Malaxa Clinical Hospital Bucharest, 022441 Bucharest, Romania
* Correspondence: claudia.mehedintu@umfcd.ro

Abstract: As the coronavirus pandemic is far from ending, more questions regarding the female reproductive system, particularly fertility issues, arise. The purpose of this paper is to bring light upon the possible link between COVID-19 and women's reproductive health. This review emphasizes the effect of SARS-CoV-2 on the hormones, endometrium and menstrual cycle, ovarian reserve, follicular fluid, oocytes, and embryos. The results showed that endometrial samples did not express SARS-CoV-2 RNA. Regarding the menstrual cycle, there is a large range of alterations, but they were all reversible within the following months. The ovarian reserve was not significantly affected in patients recovering from both mild and severe infection in most cases, except one, where the levels of AMH were significantly lower and basal follicle-stimulating hormone (FSH) levels were increased. All COVID-19 recovered patients had positive levels of SARS-CoV-2 IgG in the follicular fluid. The amount of retrieved and mature oocytes and the fertilization rate were unharmed in three studies, except for one study, where the quantity of retrieved and mature oocytes was reduced in patients with higher levels of SARS-CoV-2 antibodies. The numbers of blastocysts, top-quality embryos, and euploid embryos were affected in most of the studies reviewed.

Int. J. Environ. Res. Public Health **2022**, *19*, 984

Summary

1. Significant menstrual alterations but reversible
2. Slightly modified ovarian reserve and hormone balance
3. Reduced number and quality of embryos
4. Further investigation is needed to assess the potential impact on the live birth rate

Increased COVID-19 infections in women with polycystic ovary syndrome: a population-based study

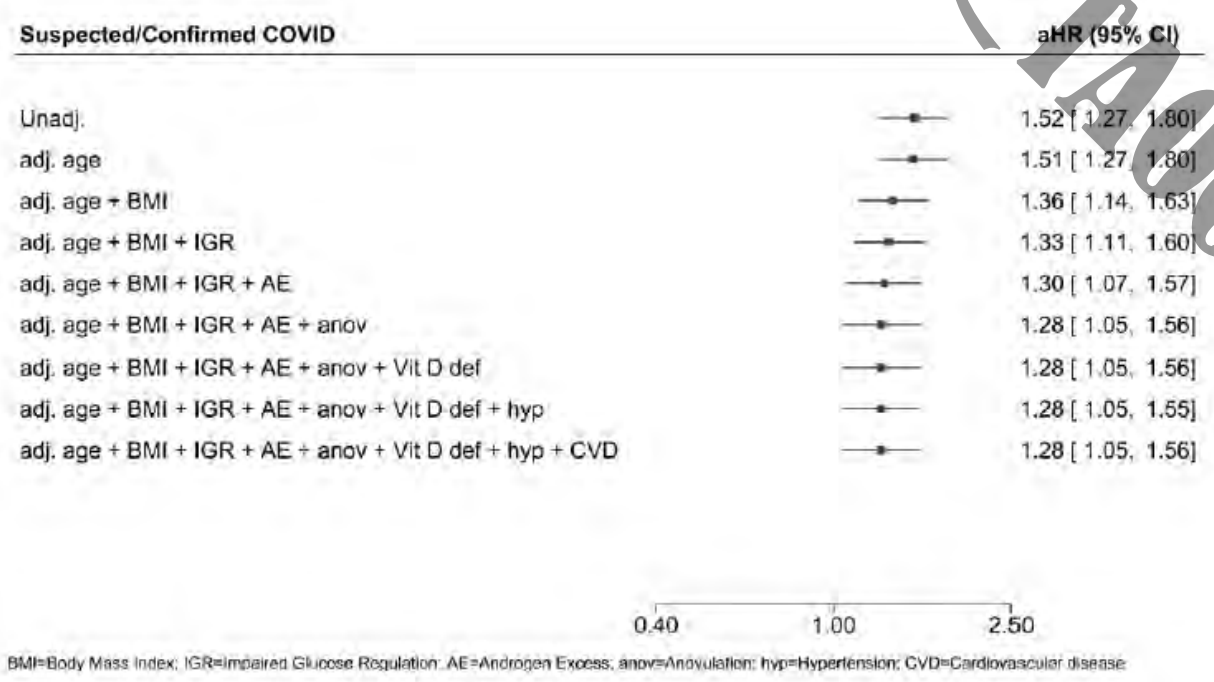
Anuradhaa Subramanian[1,*], Astha Anand[1,*], Nicola J Adderley[1], Kelvin Okoth[1], Konstantinos A Toulis[1], Krishna Gokhale[1], Christopher Sainsbury[1], Michael W O'Reilly[2,3], Wiebke Arlt[3,4] and Krishnarajah Nirantharakumar[1,5]

[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK, [2]Royal College of Surgeons in Ireland (RCSI), University of Medicine and Health Sciences, Dublin, Republic of Ireland, [3]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK, [4]National Institute for Health Research (NIHR), Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, UK, and [5]Midlands Health Data Research UK, Birmingham, UK

*(A Subramanian and A Anand contributed equally to this work)

Correspondence should be addressed to W Arlt or K Nirantharakumar
Email
w.arlt@bham.ac.uk or k.nirantharan@bham.ac.uk

Objective: Several recent observational studies have linked metabolic comorbidities to an increased risk from COVID-19. Here we investigated whether women with PCOS are at an increased risk of COVID-19 infection.
Design: Population-based closed cohort study between 31 January 2020 and 22 July 2020 in the setting of a UK primary care database (The Health Improvement Network, THIN).
Methods: The main outcome was the incidence of COVID-19 coded as suspected or confirmed by the primary care provider. We used Cox proportional hazards regression model with stepwise inclusion of explanatory variables (age, BMI, impaired glucose regulation, androgen excess, anovulation, vitamin D deficiency, hypertension, and cardiovascular disease) to provide unadjusted and adjusted hazard risks (HR) of COVID-19 infection among women with PCOS compared to women without PCOS.
Results: We identified 21 292 women with a coded diagnosis of PCO/PCOS and randomly selected 78 310 aged and general practice matched control women. The crude COVID-19 incidence was 18.1 and 11.9 per 1000 person-years among women with and without PCOS, respectively. Age-adjusted Cox regression analysis suggested a 51% higher risk of COVID-19 among women with PCOS compared to women without PCOS (HR: 1.51 (95% CI: 1.27–1.80), $P < 0.001$). After adjusting for age and BMI, HR reduced to 1.36 (1.14–1.63)], $P = 0.001$. In the fully adjusted model, women with PCOS had a 28% increased risk of COVID-19 (aHR: 1.28 (1.05–1.56), $P = 0.015$).
Conclusion: Women with PCOS are at an increased risk of COVID-19 infection and should be specifically encouraged to adhere to infection control measures during the COVID-19 pandemic.



BMI=Body Mass Index; IGR=Impaired Glucose Regulation; AE=Androgen Excess; anov=Anovulation; hyp=Hypertension; CVD=Cardiovascular disease

Table 3 Risk factors for confirmed/suspected COVID-19 from the fully adjusted model.

Risk factors	Adjusted hazard ratio	*P*-values
PCOS	1.28 (1.05–1.56)	0.015
Age category, years		
18–30	RS	RS
30–40	0.89 (0.71–1.06)	0.286
40–50	1.03 (0.82–1.29)	0.785
50–60	0.89 (0.68–1.18)	0.428
≥60	0.41 (0.23–0.74)	0.003
BMI	1.02 (1.01–1.03)	<0.001
Androgen excess	1.11 (0.83–1.50)	0.478
Anovulation	1.06 (0.84–1.35)	0.594
Impaired glucose regulation		
Absence of IGR	RS	RS
Pre-diabetes	1.31 (0.86–2.00)	0.215
Diabetes	1.36 (0.96–1.93)	0.085
Vitamin D deficiency	1.61 (1.05–2.47)	0.029
Hypertension	1.19 (0.88–1.62)	0.258
Cardiovascular disease	1.88 (1.12–3.17)	0.017

RS, reference standard.

European Journal of Endocrinology (2021) 184, 637-645.

Metabolism Open 7 (2020) 100052

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.journals.elsevier.com/metabolism-open

Renin-Angiotensin System overactivation in polycystic ovary syndrome, a risk for SARS-CoV-2 infection?

Abu Saleh Md Moin [a], Thozhukat Sathyapalan [b], Stephen L. Atkin [c], Alexandra E. Butler [a,*]

[a] Diabetes Research Center (DRC), Qatar Biomedical Research Institute (QBRI), Hamad Bin Khalifa University (HBKU), Qatar Foundation (QF), PO Box 34110, Doha, Qatar
[b] Academic Endocrinology, Diabetes and Metabolism, Hull York Medical School, Hull, UK
[c] Royal College of Surgeons in Ireland Bahrain, Adliya, Bahrain

ARTICLE INFO

Article history:
Received 1 July 2020
Received in revised form
10 August 2020
Accepted 13 August 2020
Available online 18 August 2020

Keywords:
ACE2 protein
Polycystic ovary syndrome
Renin
Angiotensinogen

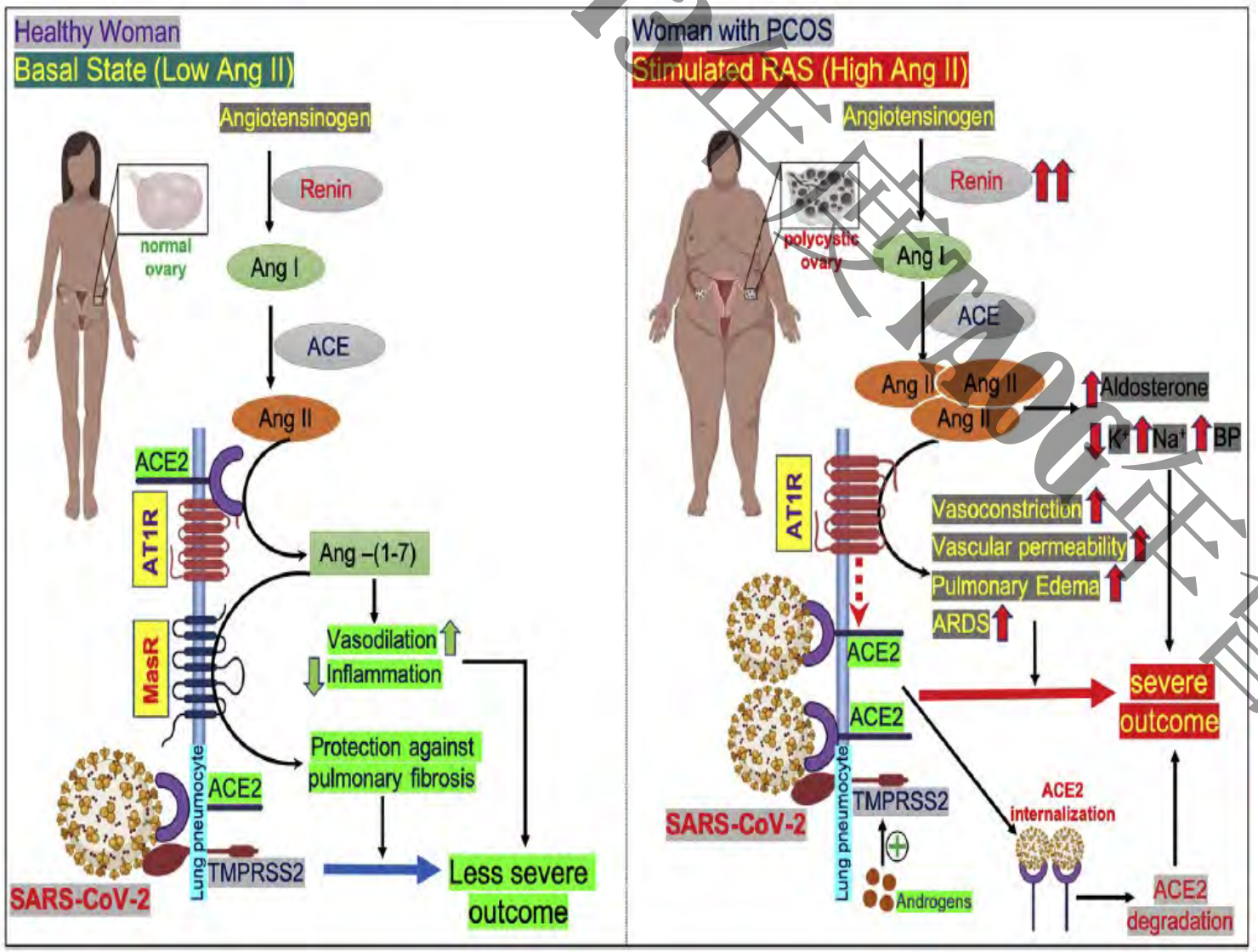
ABSTRACT

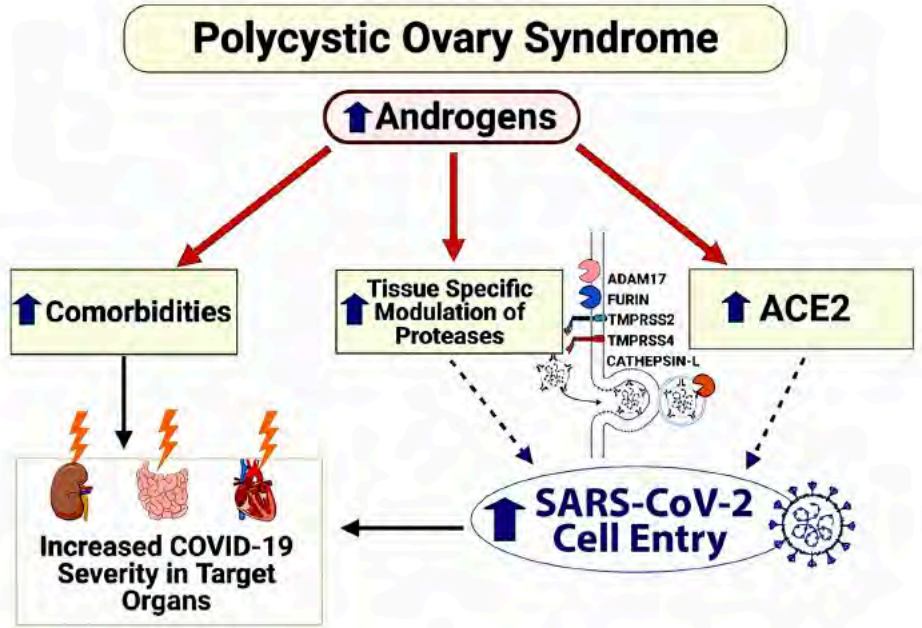
Background: The SARS-CoV-2 coronavirus gains entry to target cells via the angiotensin-converting enzyme 2 (ACE2) receptor present on cells in blood vessels, lungs, heart, intestines, and kidneys. Renin-Angiotensin System (RAS) overactivity has also been described in metabolic syndrome, type 2 diabetes (T2D) and obesity, conditions shared by women with polycystic ovary syndrome (PCOS) We hypothesized that RAS overactivity may be present in PCOS.

Methods: We determined plasma levels of RAS-related proteins in a cohort of age matched control women ($n = 97$) and women with PCOS ($n = 146$). Plasma levels of RAS-related proteins (ACE2, Renin and Angiotensinogen (AGT)) were determined by Slow Off-rate Modified Aptamer (SOMA)-scan plasma protein measurement.

Results: PCOS women had a higher BMI ($p < 0.001$), systolic ($p < 0.0001$) and diastolic ($p < 0.05$) blood pressure, waist circumference ($p < 0.0001$), testosterone ($p < 0.0001$), free androgen index ($p < 0.0001$) and CRP ($p < 0.0001$). Renin was elevated in PCOS ($p < 0.05$) and angiotensinogen was lower in PCOS ($p < 0.05$), indicating overactivity of the RAS system in PCOS. ACE2 levels were lower in PCOS ($p < 0.05$), suggesting that PCOS women are at risk for development of hypertension.

Conclusion: RAS proteins levels differed between PCOS and control women, suggesting that the insulin resistance inherent in PCOS may predispose these women to more severe COVID-19 infection.





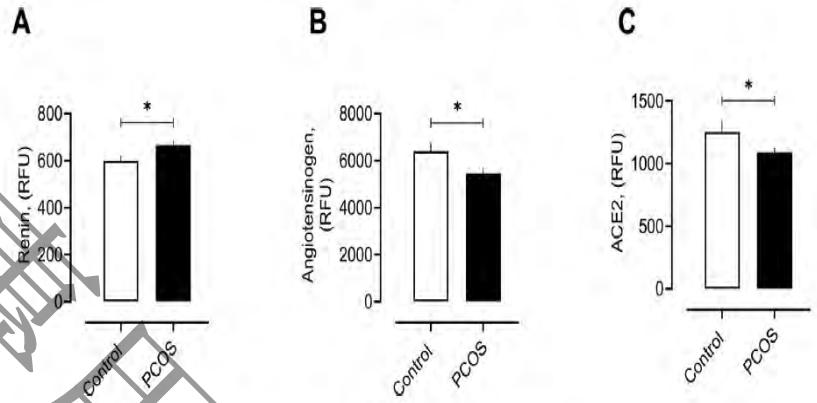


Fig. 1. RAS proteins in women with and without polycystic ovary syndrome (PCOS).
Levels of plasma Renin (A), Angiotensinogen (B) and ACE2 (C) in women with and without polycystic ovary syndrome (PCOS). RFU, relative fluorescent units. * $p < 0.05$.

frontiers | Frontiers in Endocrinology

The causal association between polycystic ovary syndrome and susceptibility and severity of COVID-19: a bidirectional Mendelian randomization study using genetic data

Yu Si, Yuye Fei, Hua Ma, Yating Xu, Li Ning, Xiu Li and Qingling Ren*

The Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China

TYPE Original Research
PUBLISHED 08 September 2023
DOI 10.3389/fendo.2023.1229900

1. MR analysis does not provide evidence supporting PCOS as a causal risk factor influencing the susceptibility or severity of COVID-19.
2. The previously observed correlation between PCOS and COVID-19 may be attributed to the influence of comorbidity factors. Such as obesity, insulin resistance, diabetes, and other cardiovascular and metabolic conditions, rather than PCOS itself, could be contributing to the association observed in these studies.

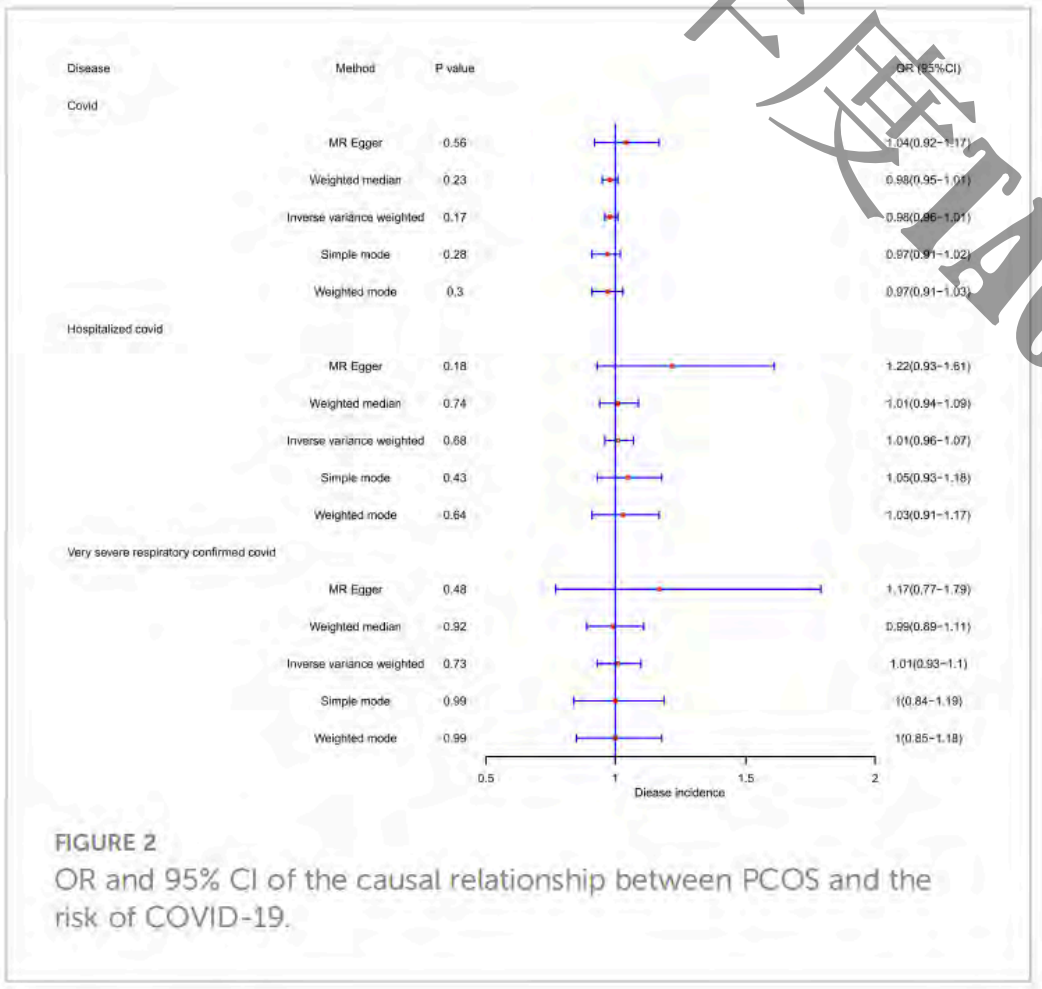


FIGURE 2
OR and 95% CI of the causal relationship between PCOS and the risk of COVID-19.

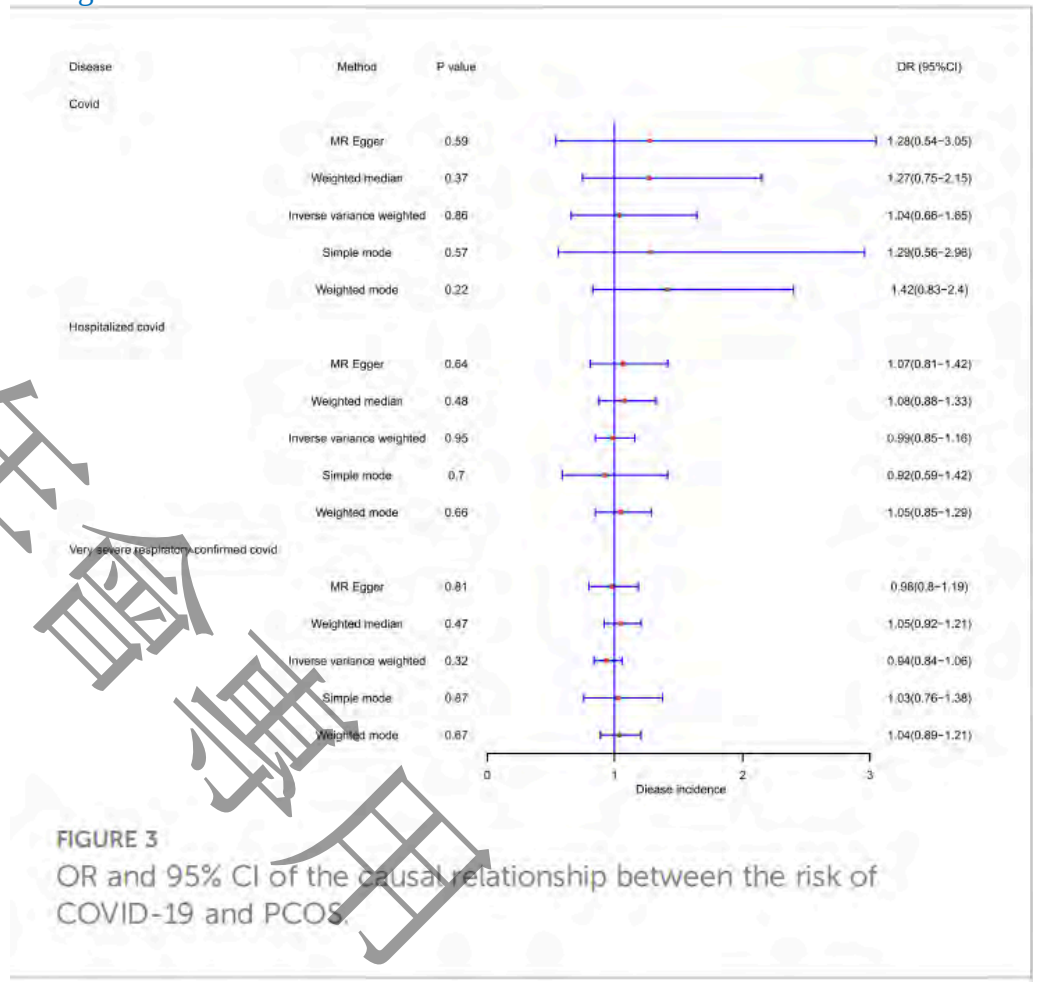


FIGURE 3
OR and 95% CI of the causal relationship between the risk of COVID-19 and PCOS.

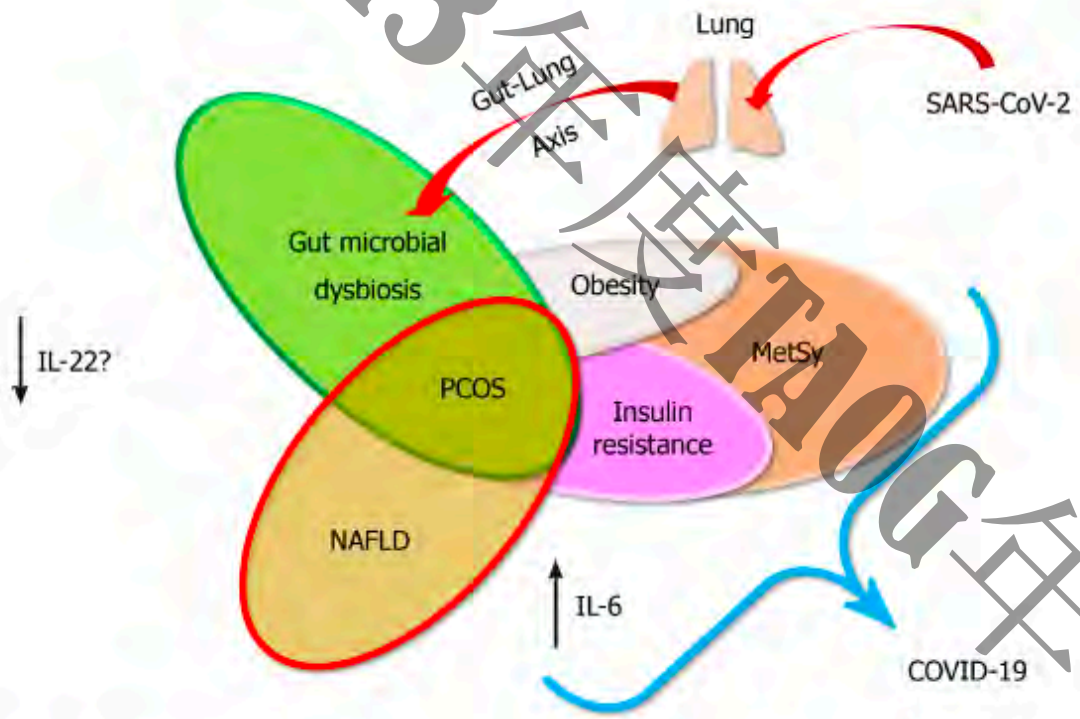


Figure 2 Polycystic ovary syndrome may increase susceptibility to coronavirus disease 2019 via its associated comorbidities (non-alcoholic fatty liver disease, metabolic syndrome, obesity, insulin resistance and alterations in the gut microbiome); the gut-lung axis is apparently implicated. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; IL-22: Interleukin 22; IL-6: Interleukin 6; PCOS: Polycystic ovary syndrome; NAFLD: Non-alcoholic fatty liver disease; COVID-19: Coronavirus disease 2019; MetSy: Metabolic syndrome.

Ioannis Ilias et al., World J Clin Cases 2021 April 26; 9(12):2711-2720

Dufailu *et al. Journal of Ovarian Research* (2021) 14:70
https://doi.org/10.1186/s13048-021-00820-1

Journal of Ovarian Research

REVIEW Open Access

COVID-19 in Africa: an ovarian victory?

Osman A. Dufailu[1†], Afrakoma Afriyie-Asante[2†], Bernard Gyan[3], David Adu Kwabena[3,4], Helena Yeboah[5], Frank Ntiakoh[6] and Meshach Asare-Werehene[7,8*]

Abstract

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) mainly attacks the respiratory system and is characterized by pneumonia, cytokine storm, coagulation disorders and severe immune downregulation. Although public health experts predicted worst outcomes in Africa, the incidence, hospitalization and mortality rates have been lower in Africa compared to other continents. Interestingly, lower incidence and mortality rates have been observed in women from Africa compared to their cohorts from other continents. Also, in the US non-Hispanic Black females have lower COVID-19 and death rates compared to their white counterparts. It's unclear why this significant difference exists; however, the ovarian function, genetics and immunological statuses could play a major role. Women of African descent have elevated levels of estrogen compared with Caucasians hence we anticipate that estrogen might offer some protection against the SARS-CoV-2 infections. The racial differences in lifestyle, age and inaccessibility to contraceptive usage might also play a role. Here, we provide insight on how the high levels of estrogen in African women might contribute to the lower cases and fatalities in Africa. Specifically, estrogen might offer protection against COVID-19 by suppressing hyper-production of cytokines, promoting anti-inflammatory cytokines, stimulating antibody production and suppressing endoplasmic reticulum (ER) stress. This will as well provide useful information on how future pandemics could be managed using Africa as a case study.

Keywords: COVID-19, SARS-CoV-2, Africa, Ovary, Mortality rate, Estrogen, Pro-inflammation cytokine

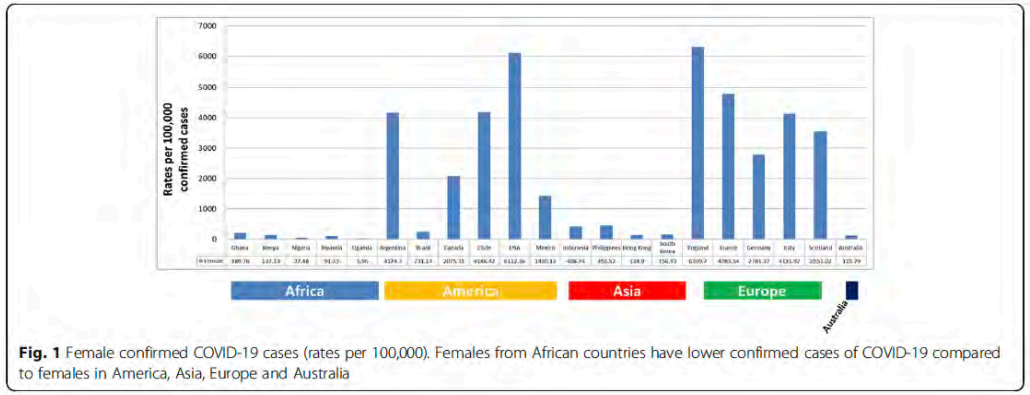


Fig. 1 Female confirmed COVID-19 cases (rates per 100,000). Females from African countries have lower confirmed cases of COVID-19 compared to females in America, Asia, Europe and Australia

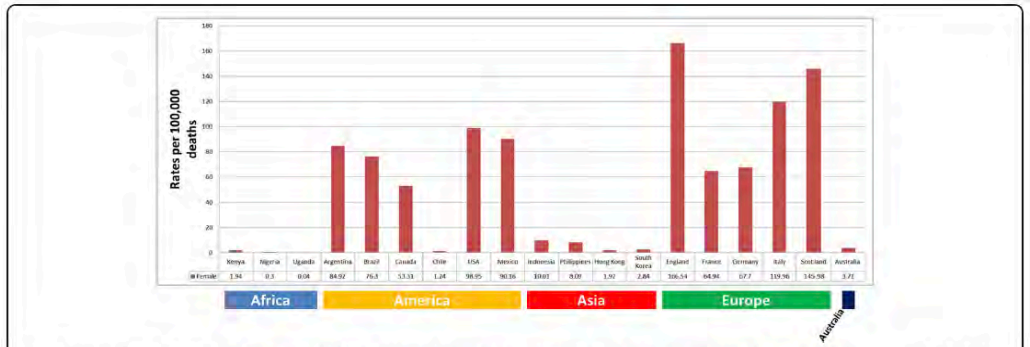


Fig. 2 Female COVID-19 Deaths (rates per 100,000). Females from African countries have lower death rate of COVID-19 compared to females in America, Asia, Europe and Australia

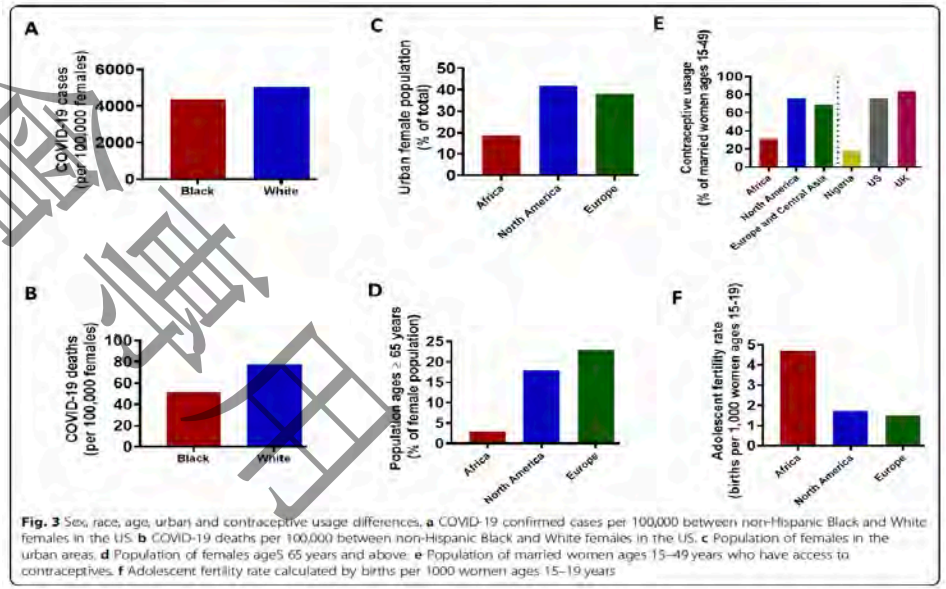


Fig. 3 Sex, race, age, urban and contraceptive usage differences. **a** COVID-19 confirmed cases per 100,000 between non-Hispanic Black and White females in the US. **b** COVID-19 deaths per 100,000 between non-Hispanic Black and White females in the US. **c** Population of females in the urban areas. **d** Population of females age≤ 65 years and above. **e** Population of married women ages 15–49 years who have access to contraceptives. **f** Adolescent fertility rate calculated by births per 1000 women ages 15–19 years

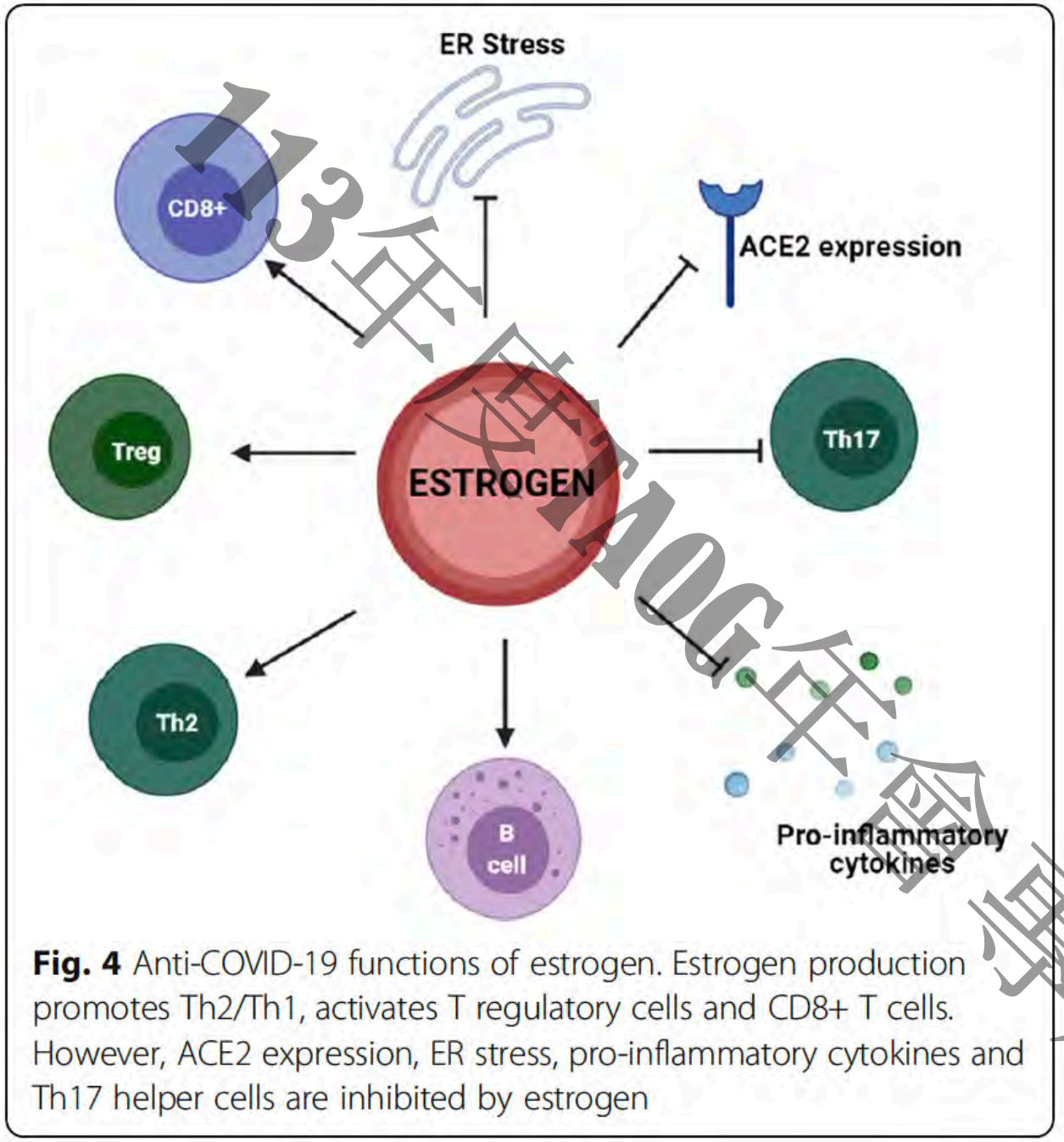


Fig. 4 Anti-COVID-19 functions of estrogen. Estrogen production promotes Th2/Th1, activates T regulatory cells and CD8+ T cells. However, ACE2 expression, ER stress, pro-inflammatory cytokines and Th17 helper cells are inhibited by estrogen

1. Eatrogen production promotes Th2/Th1, activates T regulatory cells and CD8+ T cells.
2. ACE2 expression, ER stress, proinflammatory cytokines and Th17 are inhibited by estrogen.

Outlines

1. Introduction
2. The possible mechanisms of SARS-CoV-2 infection on female fertility
3. The clinical presentations of ovarian dysfunction during and after SARS-CoV-2 infection
4. Long COVID-19 on ovarian function and female fertility
5. COVID-19 vaccination on ovarian function and female fertility
6. Take home message

Female reproductive health in Long COVID-19 (LC)

- LC Definition:

  experiencing symptoms within 3 months from the initial infection that last at least 2 months.

- Symptoms:

  fatigue, cognitive dysfunction, post-exertional malaise, headache, insomnia, muscle aches.

- Pathophysiology:

  Immune dysregulation and autoimmunity, pathogen persistence/reactivation, neurological abnormalities and neuroinflammation, tissue and organ damage, hypoperfusion and autonomic dysfunction, fibrin amyloid microclots, and microbiome dysregulation.

- Affect twice as many women as men.

- Premenopausal women have an elevated risk for LC, suggesting the sex hormones may play a key role in LC development.

frontiers | Frontiers in Rehabilitation Sciences

TYPE Mini Review
PUBLISHED 28 April 2023
DOI 10.3389/fresc.2023.1122673

Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review

Beth Pollack[1], Emelia von Saltza[2], Lisa McCorkell[2*], Lucia Santos[2], Ashley Hultman[2], Alison K. Cohen[2,3] and Letícia Soares[2*]

[1]Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, United States, [2]Patient-Led Research Collaborative, Washington, DC, United States, [3]Department of Epidemiology & Biostatistics, School of Medicine, University of California, San Francisco, San Francisco, CA, United States

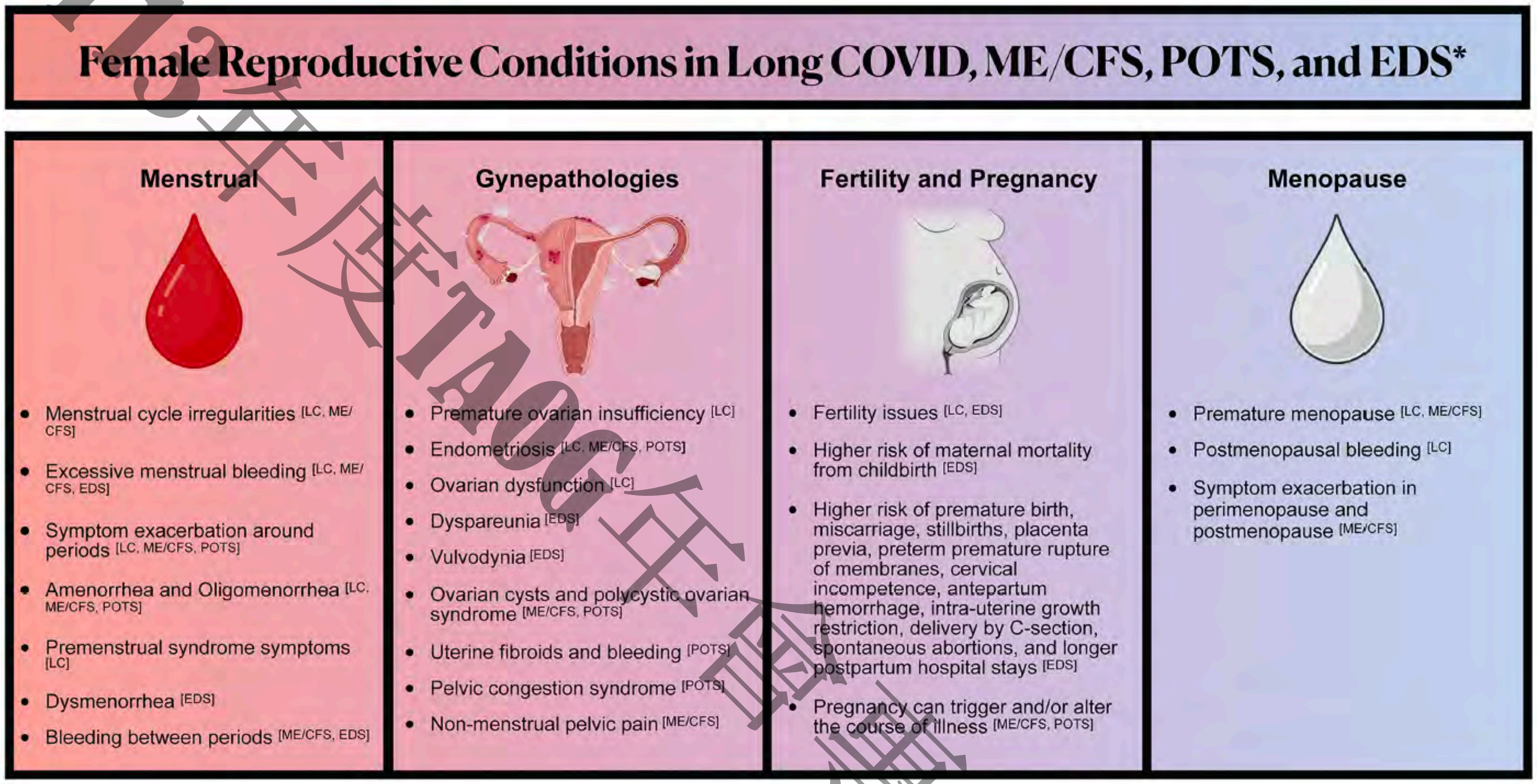


FIGURE 1
Illustrates the reproductive symptoms and conditions that may be associated with Long COVID, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), and Ehlers-Danlos Syndrome (EDS). Reproductive symptoms and conditions in illnesses associated with Long COVID are highlighted to help elucidate knowledge gaps in Long COVID reproductive health. *The lists of symptoms and conditions represented are non-exhaustive and reflect what is discussed in this literature review. There are relevant gaps in reproductive health research in all of the conditions represented.

Outlines

1. Introduction
2. The possible mechanisms of SARS-CoV-2 infection on female fertility
3. The clinical presentations of ovarian dysfunction during and after SARS-CoV-2 infection
4. Long COVID-19 on ovarian function and female fertility
5. COVID-19 vaccination on ovarian function and female fertility
6. Take home message

Human Reproduction, Vol.37, No.3, pp. 534–541, 2022
Advance Access Publication on December 22, 2021 https://doi.org/10.1093/humrep/deab282

human reproduction ORIGINAL ARTICLE Reproductive endocrinology

The effect of Covid-19 mRNA vaccine on serum anti-Müllerian hormone levels

A. Mohr-Sasson [1,2,*], J. Haas [1,2], S. Abuhasira [1], M. Sivan [1], H. Doitch Amdurski [1], T. Dadon [1], S. Blumenfeld [1,2], E. Derazne [2], R. Hemi [2,3], R. Orvieto [1,2], A. Afek [1,2], and J. Rabinovici [1,2]

[1]Department of Obstetrics and Gynecology, Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel [2]Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel [3]The Institute of Endocrinology, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel

Serum AMH levels before and 3 months following two mRNA SARS-CoV-2 vaccinations did not change significantly.

Table II Women's characteristics by age group.

	Age group			
	<30 (n = 79)	30–35 (n = 31)	≥35 (n = 19)	
	Mean ± SD Median (25th–75th percentile)	Mean ± SD Median (25th–75th percentile)	Mean ± SD Median (25th–75th percentile)	*P*
Age (years)	25.9 ± 3.1 26.0 (24.0–28.0)	32.8 ± 1.2 33.0 (32.0–34.0)	37.8 ± 1.5 38.0 (36.0–39.0)	1.2E−21
BMI (kg/m^2)	22.6 ± 3.6 22.1 (20.1–24.8)	21.4 ± 2.6 21.1 (19.6–23.2)	24.6 ± 6.4 23.4 (21.0–24.8)	0.166
Menstruation frequency (days)	28.1 ± 3.5 28.0 (28.0–30.0)	28.7 ± 4.3 28.0 (28.0–30.0)	26.9 ± 3.4 28.0 (26.0–28.0)	0.369
Menstruation length (days)	4.6 ± 1.2 5.0 (4.0–5.0)	5.2 ± 1.6 5.0 (4.0–6.0)	4.6 ± 1.5 4.0 (4.0–5.5)	0.281
AMH first (µg/l)	6.3 ± 4.6 4.9 (3.2–8.1)	4.9 ± 2.9 4.9 (2.7–6.4)	2.0 ± 1.5 1.7 (1.1–2.4)	1.5E−06
AMH second (µg/l)	6.1 ± 4.9 4.7 (2.8–7.4)	5.1 ± 3.5 4.4 (2.7–6.4)	2.1 ± 1.7 1.6 (0.6–3.3)	3.4E−05
Delta AMH(µg/l)	−0.2 ± 2.1 −0.3 (−0.9 to 0.5)	0.2 ± 1.7 0.2 (−0.6 to 0.8)	0.1 ± 0.8 −0.1 (−0.4 to 0.6)	0.288
Change (%) in AMH	−1.6 ± 28.6 −6.0 (−17.2 to 16.8)	−10.8 ± 43.9 2.9 (−13.9 to 27.4)	5.8 ± 61.5 −2.3 (−36.6 to 28.5)	0.459
Interval between AMH examination (days)	99.8 ± 12.7 94.0 (91.0–110.0)	96.8 ± 12.3 93.0 (89.0–103.0)	97.5 ± 13.4 94.0 (91.0–105.0)	0.639
Serology (S/CO)	19.8 ± 11.5 17.3 (11.6–25.5)	19.4 ± 12.4 16.8 (11.0–24.0)	14.5 ± 8.6 12.5 (8.4–23.1)	0.229

AMH, Anti-Müllerian Hormone; µg/l, microgram per liter; S/CO, signal to cutoff.

Table III Number and percent of women with a >10% decrease of anti-Müllerian hormone (AMH) levels following inoculation by age groups.

		Number (percent) of women with change in AMH						
		>10% decrease		No. or ≤10% decrease		Total		
		n	%	n	%	n	%	*P* value
Age groups	<30	33	41.77	46	58.23	79	100.00	0.63
	30–35	10	32.26	21	67.74	31	100.00	
	>35	8	42.11	11	57.89	19	100.00	

JAMA Network Open

Research Letter | Obstetrics and Gynecology

Comparison of Female Ovarian Reserve Before vs After COVID-19 Vaccination

Liubin Yang, MD, PhD; Samantha Neal, BS; Tiffany Lee, BS; Andrew Chou, MD, MSCI; Amy K. Schutt, MD, MSCI; William Gibbons, MD

Table 1. Baseline Demographic Values Between the Prevaccination and Postvaccination Groups

Characteristic	Patient group		P value[a]
	Prevaccination	Postvaccination	
AMH study			
No. of patients	836	138	NA
Age, mean (SD), y	34.2 (4.7)	35.1 (4.6)	.07
BMI, median (IQR)	26.2 (23.0-32.0)	25.1 (22.0-30.2)	.06
HbA_{1c} level, median (IQR), %	5.1 (4.9-5.4)	5.1 (4.9-5.3)	.28
AMH level, median (IQR), ng/mL	2.6 (1.2-5.0)	4.2 (1.6-8.8)	.001
AFC study			
No. of patients	1081	141	NA
Age, mean (SD), y	34.1 (4.6)	35.0 (5.1)	.03
BMI, median (IQR)	25.9 (23.0-32.0)	26.3 (23.0-32.0)	.99
HbA_{1c} level, median (IQR), %	5.1 (4.9-5.4)	5.1 (4.9-5.3)	.21
AFC, median (IQR)	18 (11-28)	20 (12-29)	.49

JAMA Network Open. 2023;6(6):e2318804. doi:10.1001/jamanetworkopen.2023.18804

JAMA Network Open

Research Letter | Obstetrics and Gynecology

Comparison of Female Ovarian Reserve Before vs After COVID-19 Vaccination

Liubin Yang, MD, PhD; Samantha Neal, BS; Tiffany Lee, BS; Andrew Chou, MD, MSCI; Amy K. Schutt, MD, MSCI; William Gibbons, MD

Table 2. Statistical Estimates of Variable Coefficients in Linear Regression Models

Vaccination status associated with outcome	Crude coefficient (95% CI)	Adjusted coefficient (95% CI)
AMH	1.777 (0.979 to 2.554)	NA
AMH covariates[a]	0.250 (0.012 to 0.488)	0.241 (−0.054 to 0.536)
AMH new assay[b]	1.276 (0.323 to 2.229)	1.401 (0.502 to 2.301)
AFC	0.035 (−2.175 to 2.245)	−0.069 (−0.322 to 0.184)

Abbreviations: AFC, antral follicle count; AMH, anti-Mullerian hormone.

[a] Refers to regression data with addition of other variables (age, body mass index, and hemoglobin A_{1c} level) with (adjusted coefficient) and without (crude coefficient) heteroskedastic correction.

[b] Represents subgroup analysis of patients who had AMH values obtained from the new AMH assay on or after 2020.

These findings suggest that COVID-19 vaccination is not associated with changes in ovarian reserve by multiple biomarker assays of AMH and AFC, supporting previous studies on AMH.[3-5] The AMH difference was not clinically significant on subgroup analysis. Study limitations include the small number of patients who received vaccination, factors associated with ovarian reserve that were not included in the study, and survival bias, as only patients who pursued fertility treatment were included. Outcomes among those who did not pursue treatment were not captured.

JAMA Network Open. 2023;6(6):e2318804. doi:10.1001/jamanetworkopen.2023.18804

Postvaccination AMH level was measured between 4 and 356 days after the first dose

RBMO
ELSEVIER

ARTICLE

The effect of SARS-CoV-2 mRNA vaccination on AMH concentrations in infertile women

BIOGRAPHY
Since 2007 Eran Horowitz has worked as a senior physician at the IVF unit, Department of Obstetrics and Gynecology, Wolfson Medical Center, Holon, and Sackler Faculty of Medicine, Tel Aviv University, Israel, where he currently holds the position of Senior Lecturer. He has published more than 40 scientific papers and book chapters.

Eran Horowitz[1,2,*], Yossi Mizrachi[1,2], Hadas Ganer Herman[1,2], Einat Oz Marcuschamer[3,4], Amir Shalev[1,2], Jacob Farhi[1,2], Elad Barber[1,2], Schwartz Harari Orna[5], Arieh Raziel[1,2], Ariel Weissman[1,2]

KEY MESSAGE

In this study COVID-19 vaccination was not associated with a short-term reduction of ovarian reserve in women undergoing IVF, and anti-Müllerian hormone concentrations were similar before and after vaccination. These findings may serve as a counselling tool for clinicians to reassure women undergoing fertility treatment that SARS-CoV-2 mRNA vaccination is safe.

ABSTRACT

Research question: Does SARS-CoV-2 mRNA vaccination affect the ovarian reserve of infertile women undergoing IVF?

Design: This was a prospective observational study at a single university-affiliated IVF unit that included infertile women aged 18–44 years who were undergoing IVF/intracytoplasmic sperm injection between November 2020 and September 2021, had received two doses of SARS-CoV-2 mRNA vaccination and had undergone measurement of baseline anti-Müllerian hormone (AMH) concentration within the 12 months preceding their recruitment. AMH concentrations before and after vaccination were evaluated and compared.

Results: Overall, 31 women were included in the study. The median AMH concentrations before and after COVID-19 vaccine were comparable (1.7 versus 1.6 g/ml, respectively, $P = 0.96$). No correlation was found between the participant's anti-COVID-19 antibody titre and the change in AMH concentration.

Conclusions: SARS-CoV-2 mRNA vaccination does not adversely affect ovarian reserve, as shown by comparing serum AMH concentrations before and after vaccination. These findings may serve as a counselling tool for clinicians to reassure women undergoing fertility treatment that SARS-CoV-2 mRNA vaccination is safe.

Original Research

In Vitro Fertilization and Early Pregnancy Outcomes After Coronavirus Disease 2019 (COVID-19) Vaccination

Devora Aharon, MD, Matthew Lederman, MD, Atoosa Ghofranian, MD, Carlos Hernandez-Nieto, MD, Chelsea Canon, MD, William Hanley, BA, Dmitry Gounko, MA, Joseph A. Lee, BA, Daniel Stein, MD, Erkan Buyuk, MD, and Alan B. Copperman, MD

OBSTETRICS & GYNECOLOGY @greenjrnl

From the Department of Obstetrics, Gynecology, and Reproductive Sciences, Icahn School of Medicine at Mount Sinai, Reproductive Medicine Associates of New York, and the Department of Obstetrics, Gynecology, and Reproductive Sciences, Mount Sinai West, New York, New York.

新光醫院李毅評主任提供

Table 1. Baseline Demographics, Cycle Characteristics, and Cycle Outcomes Among Vaccinated and Unvaccinated Patients Undergoing Controlled Ovarian Hyperstimulation

Variable	Vaccinated (n=222)	Unvaccinated (n=983)	*P*
Age (y)	36.7±4.4	37.1±4.5	.19
BMI (kg/m²)	24.3±4.6	24.9±5.0	.30
AMH (ng/mL)	2.9±2.9	2.7±2.6	.38
AFC	14.9±10.1	13.9±8.5	.33
Gravidity	0.0 (0.0–7.0)	0.0 (0.0–8.0)	.30
Parity	0.0 (0.0–3.0)	0.0 (0.0–4.0)	.01
Stimulation protocol			.02
Antagonist	92.3	86.2	.01
Flare	6.3	12.8	.005
Down-regulation	1.4	1.0	.71
Cumulative gonadotropin dosage (international units)	3,954.0±1,392.5	3,927.3±1,317.9	.78
Estradiol at trigger (pg/mL)	2,559.4±1,371.2	2,513.7±1,256.1	.91
Embryo biopsy for PGT-A	79.7	78.6	.72
Average biopsy day*			.28
5	59.9	54.2	
6	36.7	40.1	
7	3.4	5.7	
Fertilization rate (%)	80.7 [78.4–83.0]	78.7 [77.5–80.0]	.39
No. of eggs retrieved	15.9 [14.4–17.5]	15.0 [14.4–15.6]	.64
No. of mature oocytes retrieved	12.2 [11.0–13.3]	11.2 [10.7–11.7]	.20
Mature oocytes ratio (%)	77.2 [75.0–79.3]	74.7 [73.5–75.8]	.18
Blastulation rate (%)	62.9 [59.4–66.4]	60.0 [58.2–61.7]	.30
Euploid rate (%)*	48.8 [44.1–53.6]	42.5 [40.2–44.9]	.02

《Obstet Gynecol . 2022 Apr 1;139(4)》

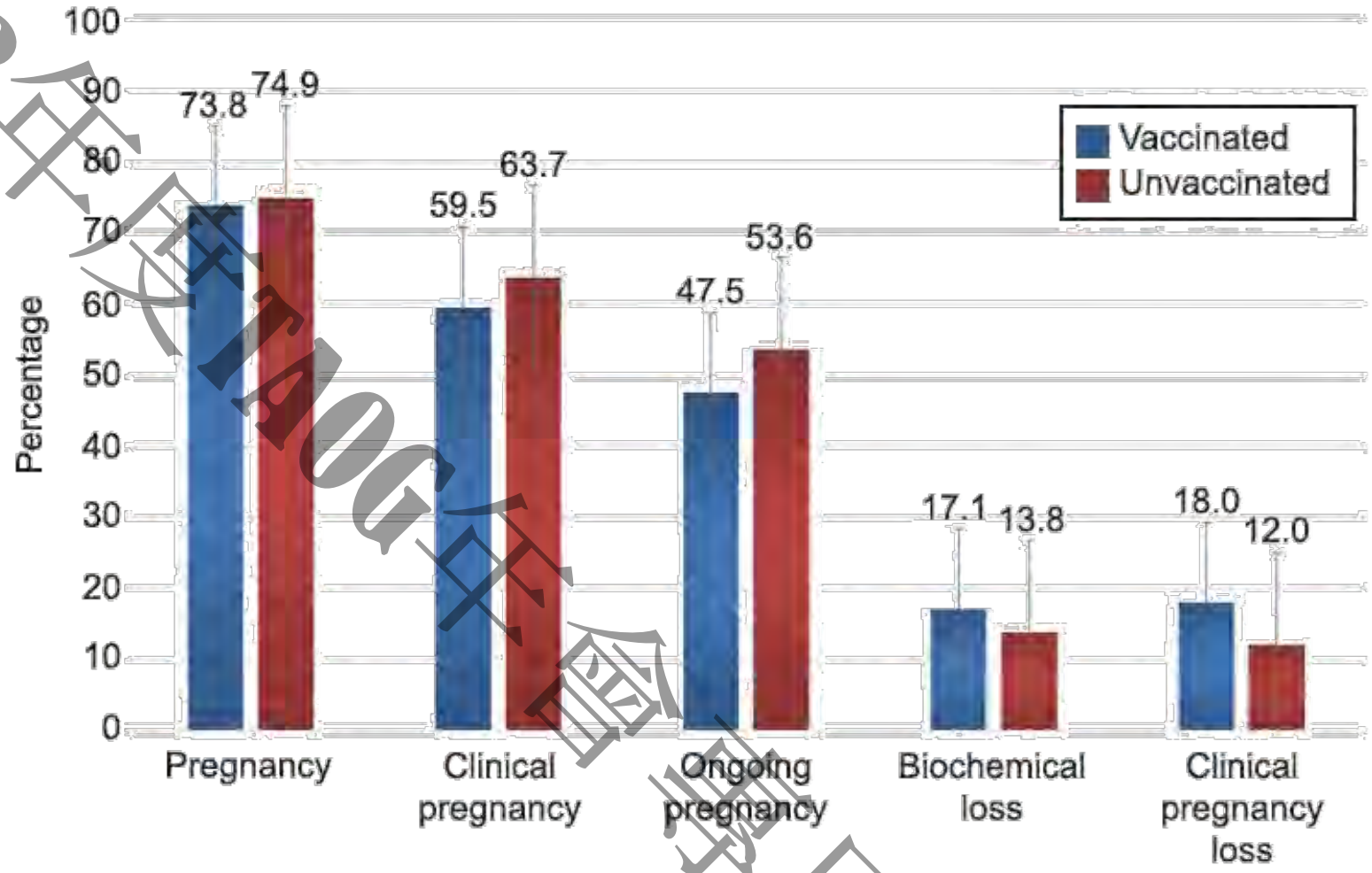


Fig. 2. Single euploid frozen-thawed embryo transfer outcomes between fully vaccinated and unvaccinated patients. *Error bars* represent 95% CIs.

Aharon. COVID-19 Vaccination and IVF Outcomes. Obstet Gynecol 2022.

《Obstet Gynecol . 2022 Apr 1;139(4)》

COVID-19 Vaccination & IVF

- Patients fully vaccinated with a COVID-19 mRNA vaccine were compared with unvaccinated patients who cycled during the same time period.
- Administration of COVID-19 mRNA vaccines was not associated with an adverse effect on IVF outcomes.
- Our findings showed the safety of COVID-19 vaccination in women who are trying to receive IVF treatment.

《Obstet Gynecol . 2022 Apr 1;139(4)》

Journal of Assisted Reproduction and Genetics (2022) 39:1849–1859
https://doi.org/10.1007/s10815-022-02543-8

REPRODUCTIVE PHYSIOLOGY AND DISEASE

Effects of COVID-19 vaccination status, vaccine type, and vaccination interval on IVF pregnancy outcomes in infertile couples

Meng Dong[1,2,3] · Shanshan Wu[1,2] · Xue Zhang[3] · Na Zhao[1,2] · Jing Qi[1,2] · Dandan Zhao[1,2] · Yang Sang[1,2] · Jichun Tan[1,2]

Received: 26 April 2022 / Accepted: 7 June 2022 / Published online: 27 June 2022

Abstract

Purpose This study aimed to explore whether the coronavirus disease (COVID-19) vaccination of both partners in infertile couples, different types of COVID-19 vaccines, and the interval between complete vaccination and oocyte retrieval or embryo transfer (ET) affect the quality of embryos and pregnancy rates in in vitro fertilization (IVF).

Methods This was a prospective cohort study, comprising 735 infertile couples conducted between December 6, 2021, and March 31, 2022, in a single university hospital-based IVF center. The patients were divided into different groups according to the vaccination status of both partners in infertile couples, type of vaccine, and interval between complete vaccination and IVF treatment. The embryo quality and pregnancy rates were compared among different groups.

Results The results showed that embryo quality and pregnancy rates had no significant differences among different groups. The multivariate regression model showed that the vaccination status of both infertile couples, types of vaccines, and intervals had no significant effects on the clinical pregnancy rate.

Conclusions The vaccination status of both partners in infertile couples, different types of vaccines, and time intervals have no effect on embryo quality and pregnancy rates in IVF. This is the first study to compare the vaccination status of both partners in infertile couples and the impact of different vaccine types on pregnancy rates and embryo quality in detail. Our findings provide evidence of vaccine safety for infertile couples wishing to undergo IVF treatment. This evidence is crucial for decision-making by clinicians and policymakers involved in IVF cycles.

scientific reports

OPEN

COVID-19 infection and vaccine have no impact on in-vitro fertilization (IVF) outcome

Soha Albeitawi[1✉], Zina M. Al-Alami[2], Jehan Hamadneh[3], Hiba Alqam[1], Hussein Qublan[4] & Maha Al Natsheh[5]

To investigate the effect of COVID-19 infection or vaccine on IVF outcome. This is a multicenter retrospective study. Data were collected from all patients treated in the ART units between September and November 2021 after the vaccination of the general population began. Medical records of all patients who had IVF/intracytoplasmic sperm injection (ICSI) were retrospectively reviewed. Patients were categorized into four groups: previously infected by COVID-19, vaccinated by COVID vaccine, previously infected and vaccinated, or neither infected nor vaccinated. Total number of participants 151 (vaccinated only 66, infected only 18, vaccinated and previously infected 34, and control 33. Outcomes (ET on day of trigger, number of oocytes retrieved, quality of oocytes, number of fertilized oocytes, number and quality of embryos, number of embryos transferred, number of embryos frozen, implantation rate and clinical pregnancy rate) were compared between these four groups. Moreover, we compared the outcome before and post infection, as well as before and post vaccine in a group of patients. No evidence was found to suggest that COVID-19 disease or SARS-CoV-2 Vaccine adversely affects Clinical pregnancy rates (positive fetal heartbeat) (OR 0.9, CI 0.5–1.9, OR 1.8, CI 0.9–3.6, respectively) and the following parameters: fertilization rate, implantation rate, positive bHcg) (OR 0.9, CI 0.5–1.8, OR 1.5, CI 0.7–2.9, respectively). Although a limitation of our study is the small comparison groups, and the wide confidence intervals in the Odds Ratio estimates.

Topic	**Reproductive endocrinology (incl. ovarian reserve testing, ovarian stimulation, IVM, POI, PCOS, infancy, disorders of sexual development, puberty, adolescence, menopause)**
Presentation preference	**Oral presentation or poster**
Abstract title	**Follicle-stimulating hormone significantly upregulates the expressions of angiotensin-converting enzyme 2 and angiotensin II type I receptor in ovarian follicles during stimulation cycles**
Biography	**Dr. Tsung-Hsuan Lai, head of Cathay General Hospital's Assisted Reproductive Center and Associate Professor at Fu-Jen Catholic University, specializes in reproductive endocrinology and infertility. A 1997 National Cheng Kung University Medicine graduate, he holds a 2018 Ph.D. in Bioinformatics and Systems Biology from National Central University. With a Fulbright Scholarship, he studied infertility at Johns Hopkins. His clinical expertise spans from IVF to robotic surgery, with active roles in Taiwanese medical societies (TAOG, TSRM) and editorial contributions to renowned journals.**

T.H. Lai[1,2], S.H. Chiu[3], W.B. Wu[3,2].
[1]Cathay General Hospital, REI division- OBGYN, Taipei, Taiwan R.O.C..
[2]School of Medicine- Fu Jen Catholic University, Medicine, New Taipei City, Taiwan R.O.C..
[3]School of Medicine- Fu Jen Catholic University, Graduate Institute of Biomedical and Pharmaceutical Science, New Taipei City, Taiwan R.O.C..

Study question:

What is the effect of gonadotropins on the expressions of angiotensin-converting enzyme 2 and angiotensin II type I receptor in ovarian follicles and granulosa cells?

Summary answer:

Follicle-stimulating hormone (FSH) significantly upregulates ACE2 and AT1R expressions in murine ovarian follicles and granulosa cells, mediated through PI3K-Akt-NF-κB p65 signaling pathways.

1. Exogeneous FSH significantly upregulates ACE2 and AT1R during COH.
2. PI3K-Akt-NF-kB p65 signaling pathway

Cryobiology 103 (2021) 1–6

Contents lists available at ScienceDirect

Cryobiology

journal homepage: www.elsevier.com/locate/cryo

Review

High cryo-resistance of SARS-CoV-2 virus: Increased risk of re-contamination at transplantation of cryopreserved ovarian tissue after COVID-19 pandemic

Vladimir Isachenko *, Evgenia Isachenko, Peter Mallmann, Gohar Rahimi

Department of Obstetrics and Gynecology, University Maternal Hospital, Cologne University, Cologne, Germany

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Anticancer treatment
Virus
Structure
Membrane
Water
Cryopreservation
Cryostability
Virulence
Ovarian tissue transplantation
Contamination

ABSTRACT

Cryopreservation and re-transplantation of ovarian tissue after anticancer treatment is important medical technology. Today, during a pandemic, the risk of contamination of transplanted cells with SARS-CoV-2 virus is extremely high. Data about cryo-resistance (virulence and/or infectivity) of SARS-CoV-2 are limited. Analysis and systematization of literature data allow us to draw the following conclusions: 1) The cytoplasmic membrane of somatic cell, like envelope of corona viruses, consists of lipid bilayer and this membrane, like envelope of corona virus, contains membrane proteins. Thus, we can consider the cytoplasmic membrane of an ordinary somatic cell as a model of the envelope membrane of SARS-CoV-2. It is expected that the response of the virus to cryopreservation is similar to that of a somatic cell. SARS-CoV-2 is more poor-water and more protein-rich than somatic cell, and this virus is much more cryo-resistant. 2) The exposure of somatic cells at low positive temperatures increases a viability of these cells. The safety of the virus is also in direct proportion to the decrease in temperature: the positive effect of low temperatures on SARS-CoV-2 virus has been experimentally proven. 3) Resistance of SARS-CoV-2 to cryoprotectant-free cryopreservation is extremely high. The high viability rate of SARS-CoV-2 after freezing-drying confirms its high cryo-resistance. 4) The risk of SARS-CoV-2 infection after transplantation of cryopreserved ovarian tissues that have been contaminated with this virus, increases significantly. Our own experimental data on the increase in the viability of cancer cells after cryopreservation allow us to formulate a hypothesis about increasing of viability (virulence and/or infectivity) of SARS-CoV-2 virus after cryopreservation.

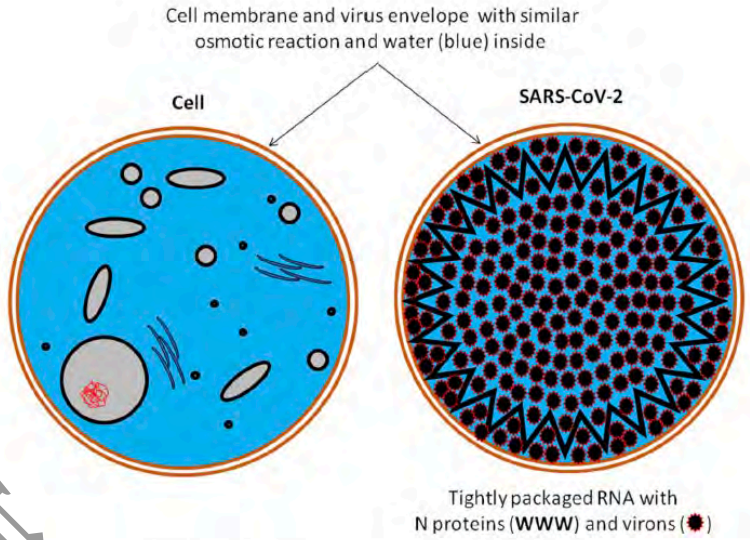


Fig. 1. Schematic representation of somatic cell and SARS-CoV-2.

Outlines

1. Introduction
2. The possible mechanisms of SARS-CoV-2 infection on female fertility
3. The clinical presentations of ovarian dysfunction during and after SARS-CoV-2 infection
4. Long COVID-19 on ovarian function and female fertility
5. COVID-19 vaccination on ovarian function and female fertility
6. Take home message

Take home message

- Up to date, data on SARS-CoV-2 infection in female fertility are limited.
- No co-expression of ACE2 and TMPRSS2 in the myometrium, uterus, ovaries or fallopian tubes, indicating no or very low susceptibility to SARS-CoV-2 infection.
- Oocytes seem to have the ACE2 and TMPRSS2 machinery to be susceptible to SARS-CoV-2 infection, but viral RNA in oocytes has not been detected so far.
- A transient impact of COVID-19 on menstrual pattern.
- Embryos and particularly late blastocysts seem to have the ACE2 and TMPRSS2 machinery to be susceptible to SARS-CoV-2 infection.
- No significant impact/ slightly modified on ovarian reserve/function or follicular fluid parameters
- Significant menstrual alterations but reversible

Take Home message

- No negative impact on ART outcomes in asymptomatic or mild SARS-CoV-19 infection females.
- No data on the minimum required interval, if any, between COVID-19 recovery and ART treatment.
- Vaccination has no negative impact on ovarian reserve/folliculogenesis/function or ART outcomes. A transient effect on the menstrual cycle has been documented.
- No influence of mRNA SARS-CoV-2 vaccine on the performance of patients during their immediate subsequent ART cycle. Pregnancy rates in post-vaccination ART cycles are similar to those in unvaccinated patients.
- Reduced number and quality of embryos
- Potential infection in freezing egg and embryos

Future research

- Is there a minimum interval between COVID-19 and ART treatment to ensure optimal outcomes?
- Does COVID-19 disease affect ovulation?
- Are the entry factors for SARS-CoV-2 co-expressed in human embryos at different developmental stages?
- Can the SARS-CoV-2 virus infect oocyte/embryos in vivo?
- Further investigation is needed to assess the potential impact of long COVID-19 on the female reproduction.
- Is there a long-term impact of COVID-19 vaccination on female/male reproductive function, including ovarian reserve?

Human Reproduction Update, Vol.29, No.2, pp. 177–196, 2023
Advance Access Publication on November 14, 2022 https://doi.org/10.1093/humupd/dmac037

human reproduction update

SARS-CoV-2, fertility and assisted reproduction

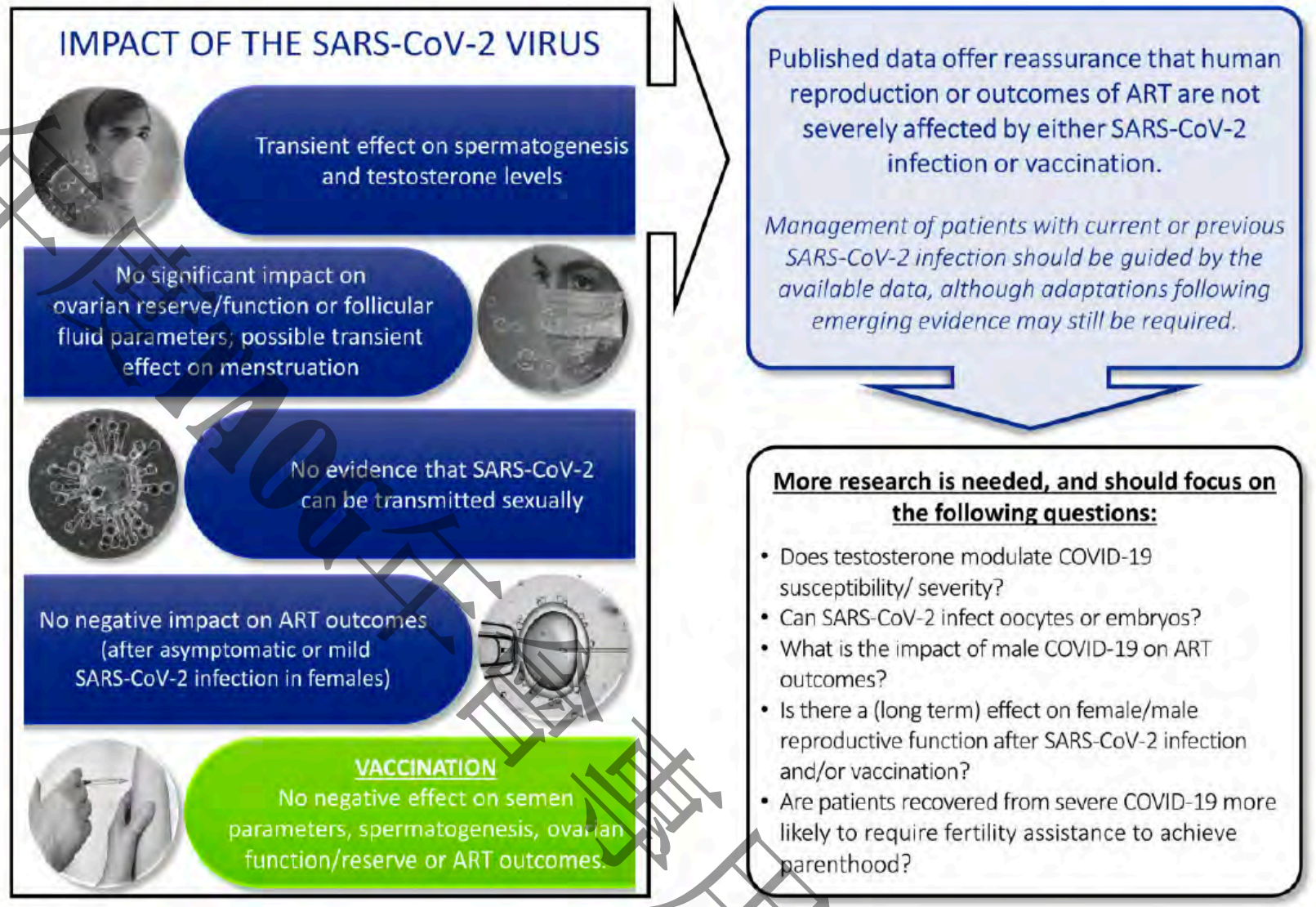
Baris Ata [1,2,†], Nathalie Vermeulen [3,†], Edgar Mocanu [4], Luca Gianaroli [5], Kersti Lundin [6], Satu Rautakallio-Hokkanen [7], Juha S. Tapanainen [8,9], and Anna Veiga [10,*]

[1]Obstetrics and Gynecology Department, Koc University, Istanbul, Turkey [2]ART Fertility Clinics, Dubai, United Arab Emirates [3]ESHRE Central Office, Strombeek-Bever, Belgium [4]Department of Reproductive Medicine, Rotunda Hospital and Royal College of Surgeons in Ireland, Dublin, Ireland [5]Società Italiana Studi di Medicina della Riproduzione, S.I.S.Me.R. Reproductive Medicine Institute, Bologna, Emilia-Romagna, Italy [6]Reproductive Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden [7]Fertility Europe (No Dept), Evere, Belgium [8]Department of Obstetrics and Gynaecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland [9]Department of Obstetrics and Gynaecology, Oulu University Hospital and Medical Research Centre PEDEGO Research Unit, Oulu, Finland [10]Barcelona Stem Cell Bank, IDIBELL Programme for Regenerative Medicine, Barcelona, Spain

*Correspondence address. Barcelona Stem Cell Bank, Regenerative Medicine Programme, Institut d'Investigació Biomèdica de Bellvitge. IDIBELL Hospital Duran i Reynals—3a planta, Gran Via de l'Hospitalet, 199-203, 08908 L'Hospitalet de Llobregat, Barcelona, Spain. E-mail: aveiga@idibell.catguidelines@eshre.eu https://orcid.org/0000-0002-0943-9904

Submitted on June 13, 2022; resubmitted on September 15, 2022; editorial decision on October 20, 2022

GRAPHICAL ABSTRACT



The review summarizes the data concerning the SARS-CoV-2 virus, COVID-19 and SARS-CoV-2 vaccination and its impact on human gametes, endocrinological processes, reproduction and fertility.