

Covid-19 Impact on Reproductive and Adrenal Hormones

Mark Newman, MS



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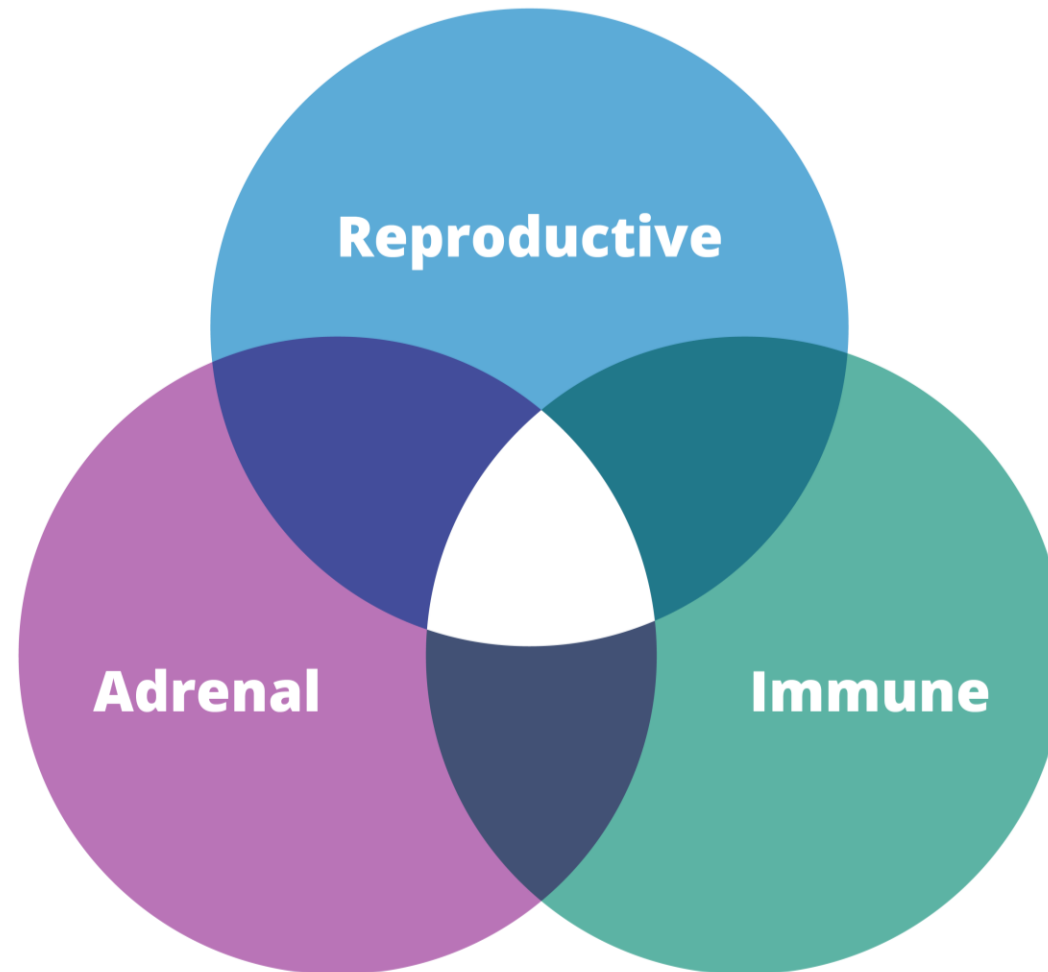


Disclaimer

This lecture and the cited scientific literature, when referring to women/females, are referring to individuals born biological females; when referring to men/males, this lecture is referring to individuals born biological males.



Complex Problems Need Comprehensive Solutions



Serum

- Estrogen (production)
- Testosterone (production)
- DHEA (production)
- Progesterone (production)

Saliva

- Cortisol (free pattern)



Dried Urine

- Estrogen (production)
- Estrogen (metabolism)
- Estrogen (methylation)

Serum

- Estrogen (production)
- Testosterone (production)
- DHEA (production)
- Progesterone (production)

Saliva

- Cortisol (free pattern)



Peer-Reviewed Published Validation

- **Estradiol, Estrone, Progesterone Metabolites – BMC Chemistry (2019)**
 - Dried urine and **serum correlation**
 - Dried urine and **24-hour urine correlation**
 - Dried urine and **liquid urine correlation**
- **Estrogen & Androgen Metabolites, Melatonin, OATs – BMC Chemistry (2021)**
 - Dried urine and 24-hour urine correlation, estrogen/androgen metabolites and melatonin
 - Dried urine and liquid urine correlation, estrogen/androgen metabolites, melatonin, OATs



Dried Urine

- Estrogen (production)
- Estrogen (metabolism)
- Estrogen (methylation)
- Testosterone (production)
- Testosterone (metabolism)
- DHEA (production)
- DHEA (metabolism)
- Progesterone (production)
- ?
- Cortisol (production)
- Cortisol (metabolism)
- B6, B12, Glut. deficiency
- Neurotransmitter balance
- Oxidative stress
- Melatonin (production)

Serum

- Estrogen (production)
- Testosterone (production)
- DHEA (production)
- Progesterone (production)

Saliva

- Cortisol (free pattern)



Dried Urine

- Estrogen (production)
- Estrogen (metabolism)
- Estrogen (methylation)
- Testosterone (production)
- Testosterone (metabolism)
- DHEA (production)
- DHEA (metabolism)
- Progesterone (production)
- **Cortisol (free pattern)**
- Cortisol (production)
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- **Urine and Salivary Cortisol, Cortisol Metabolites – J. Clin. Transl. Endoc. (2020)**
 - Dried urine and 24-hour urine correlation, free cortisol/cortisone
 - **Diurnal cortisol from dried urine and saliva correlate** (68 individuals collected both on the same day)
 - Dried urine and 24-hour urine correlation, cortisol metabolites
 - Dried urine and liquid urine correlation, cortisol and metabolites



Dried Urine

- Estrogen (production)
- Estrogen (metabolism)
- Estrogen (methylation)
- Testosterone (production)
- Testosterone (metabolism)
- DHEA (production)
- DHEA (metabolism)
- Progesterone (production)
- Cortisol (free pattern)
- Cortisol (production)
- Cortisol (metabolism)
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- Neurotransmitter balance
- Oxidative stress
- Melatonin (production)

DUTCH Complete

Serum

- Estrogen (production)
- Testosterone (production)
- DHEA (production)
- Progesterone (production)

Saliva

- Cortisol (free pattern)



Dried Urine

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- Estrogen (metabolism)
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DUTCH Complete

Serum

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- Testosterone (production)
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- Progesterone (production)

Saliva

- Cortisol (free pattern)
- Cortisol (CAR)

DUTCH Plus



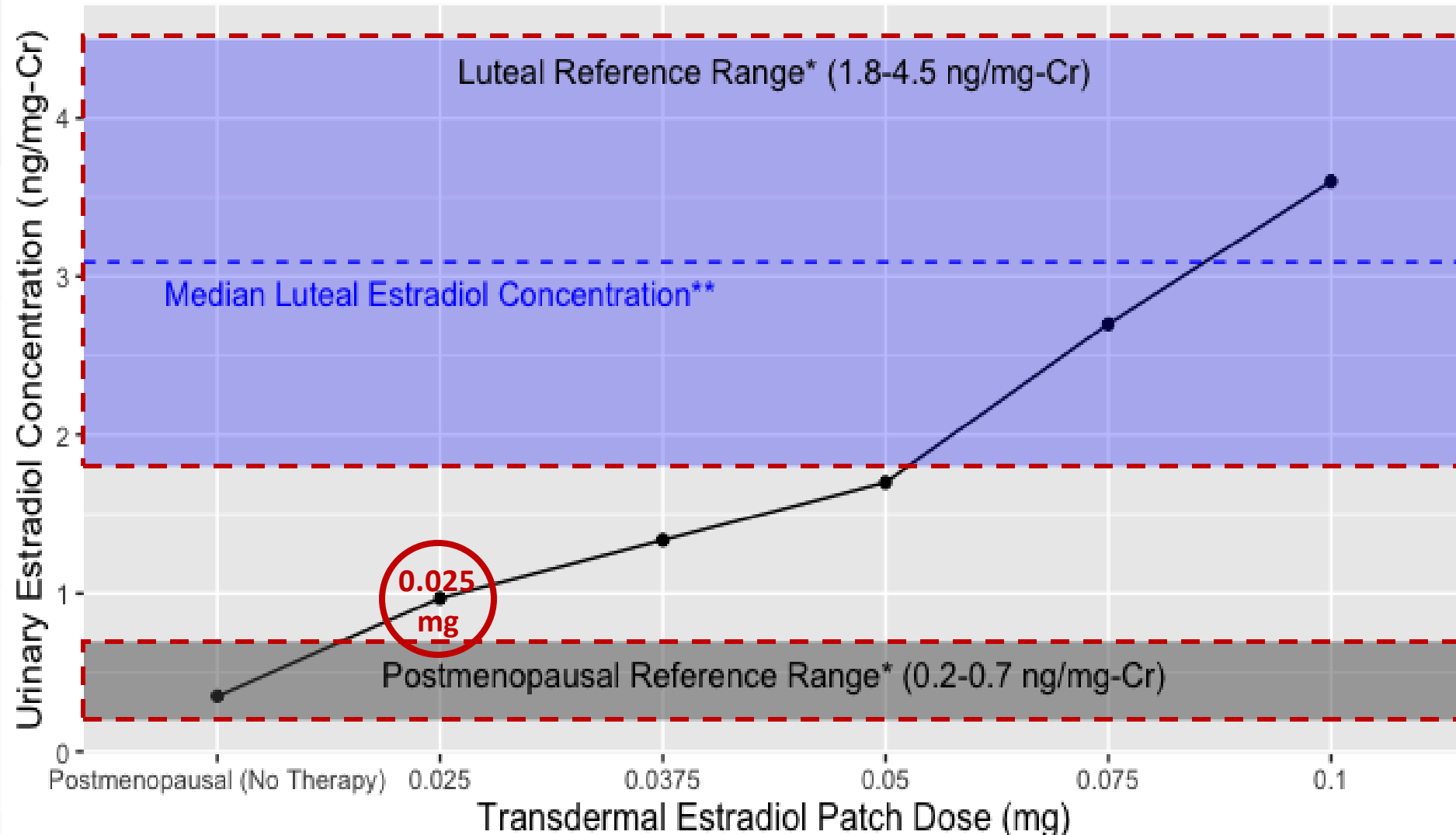
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- **Monitoring HRT – Patches, Creams, Gels, with dose-dependent responses (NAMS, 2021)**
 - **HRT correlation** with dosage and general agreement with reported clinical changes
 - Abstracts (x3) accepted on estradiol patches, gels, and a three-way comparison with creams



Accepted for publication (NAMS 2021)

Median Estradiol Concentrations by Dose



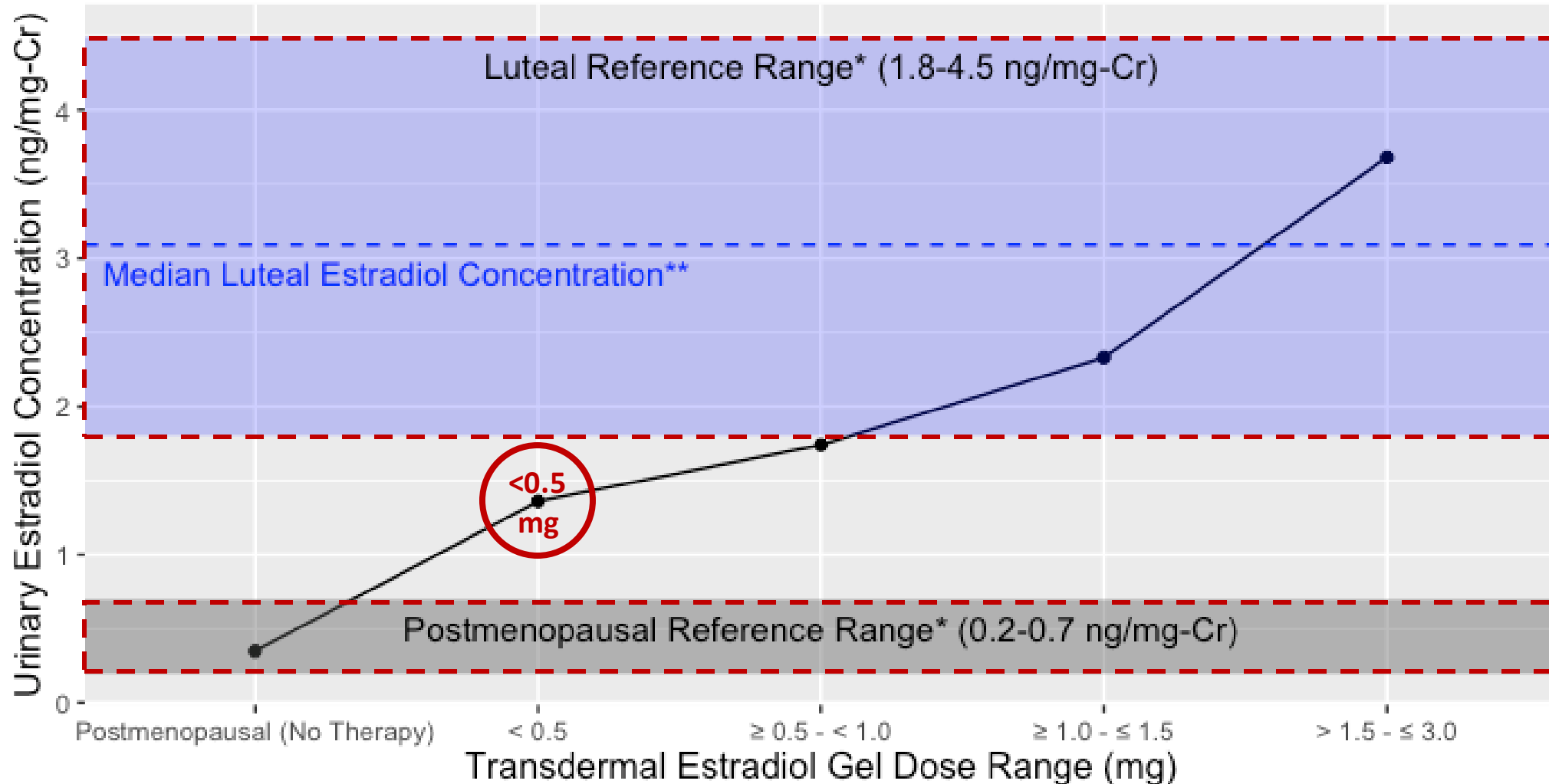
*Reference ranges are those established by Precision Analytical, a CLIA-certified clinical laboratory.

**Median luteal estradiol concentration of premenopausal women included in the study



Accepted for publication (NAMS 2021)

Median Estradiol Concentrations by Dose Range

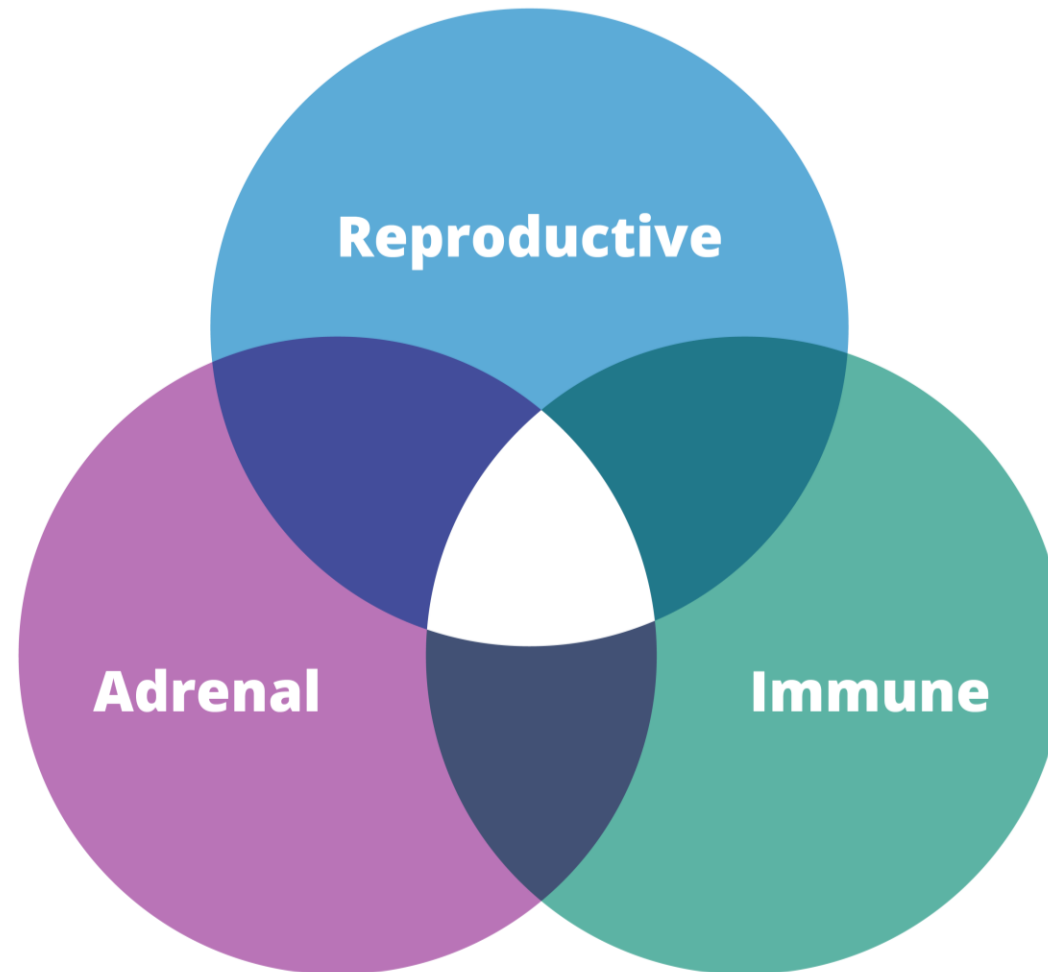


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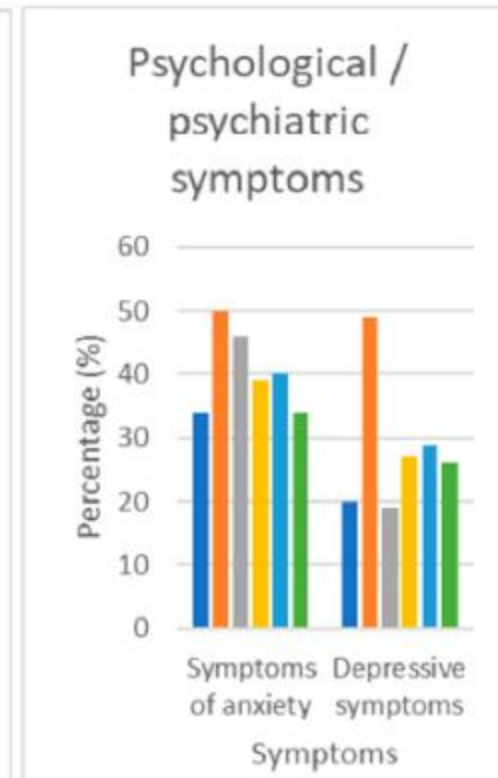
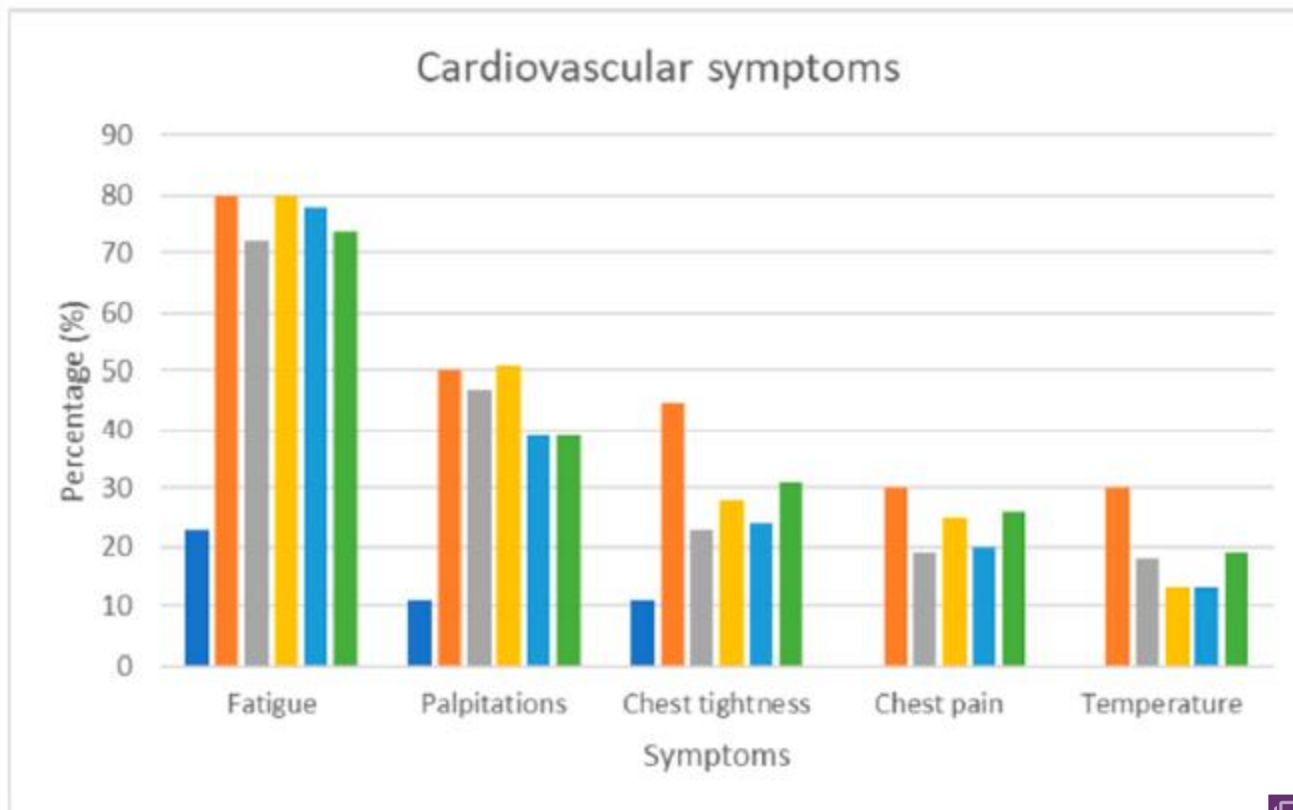


Complex Problems Need Comprehensive Solutions



LONG-COVID SYMPTOMS

- Never been tested positive
- Currently positive
- Negative for less than a month
- Negative for at least a month
- Negative for at least two months
- Negative for at least three months



Article

Long-COVID Syndrome? A Study on the Persistence of Neurological, Psychological and Physiological Symptoms

Graziella Orrù ^{1,*}, Davide Bertelloni ¹, Francesca Diolaiuti ¹, Federico Mucci ², Mariagrazia Di Giuseppe ¹, Marco Biella ¹, Angelo Gemignani ¹, Rebecca Ciacchini ¹ and Ciro Conversano ¹

LONG-COVID SYMPTOMS

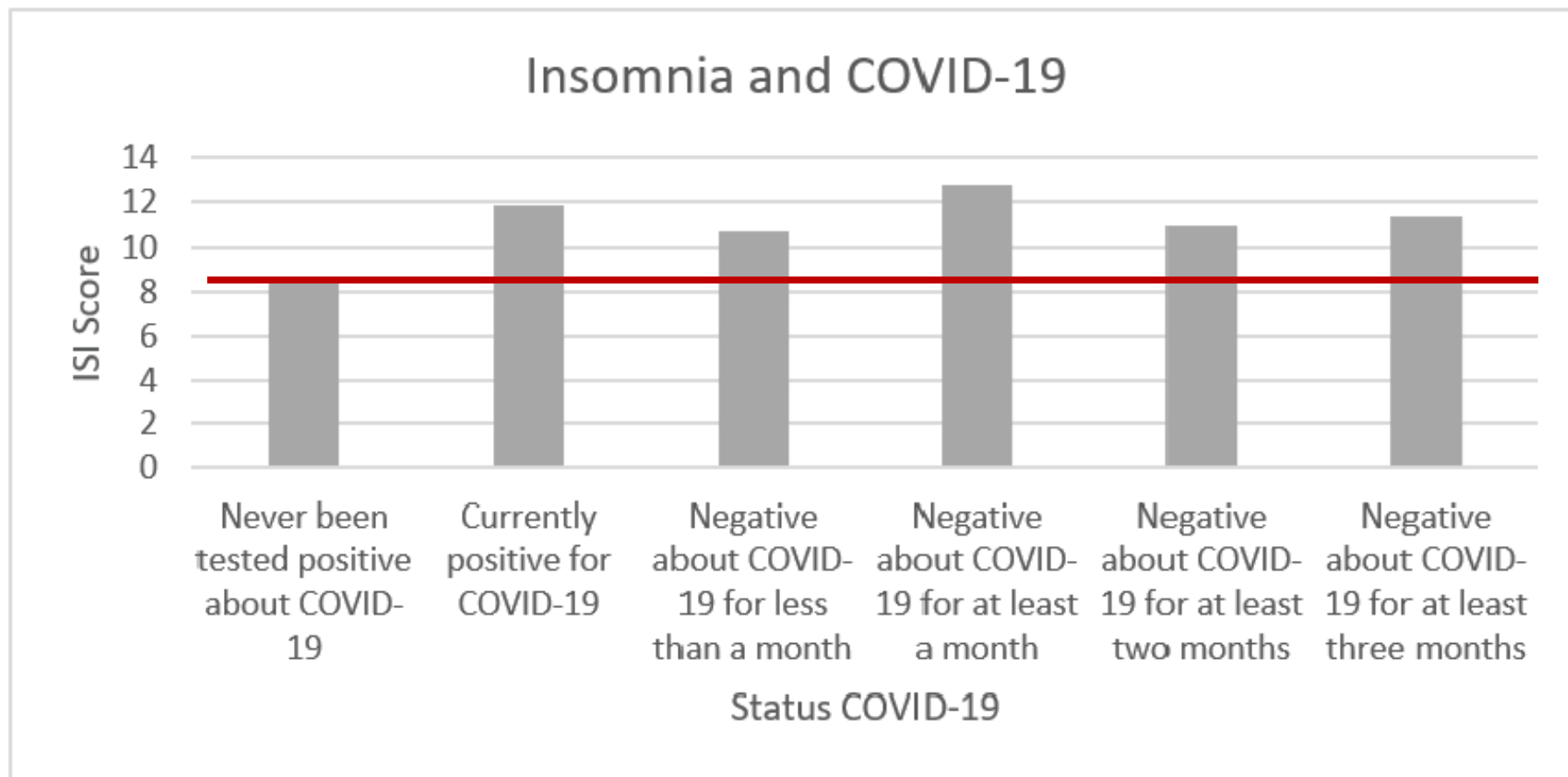
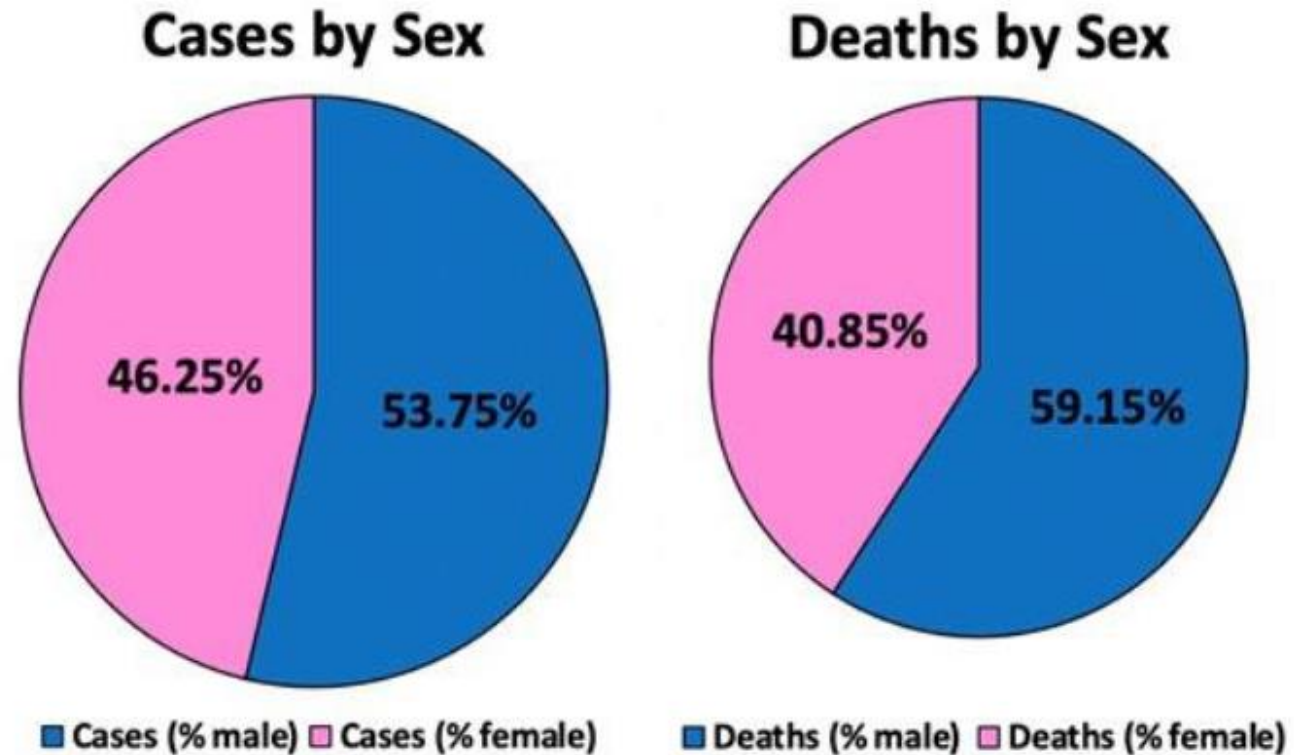


Figure 3. The mean values of the scores indicated by the subjects regarding their insomnia (ISI score) are reported, stratified by COVID-19 status.

COVID: Who's Getting It? Who's Dying?

- Men get Covid more often and have higher fatality rates



COVID: Who's Getting It? Who's Dying?

- Men have higher fatality rates

CAGNACCI AND XHOLLI
Menopause, Vol. 28, No. 5, 2021

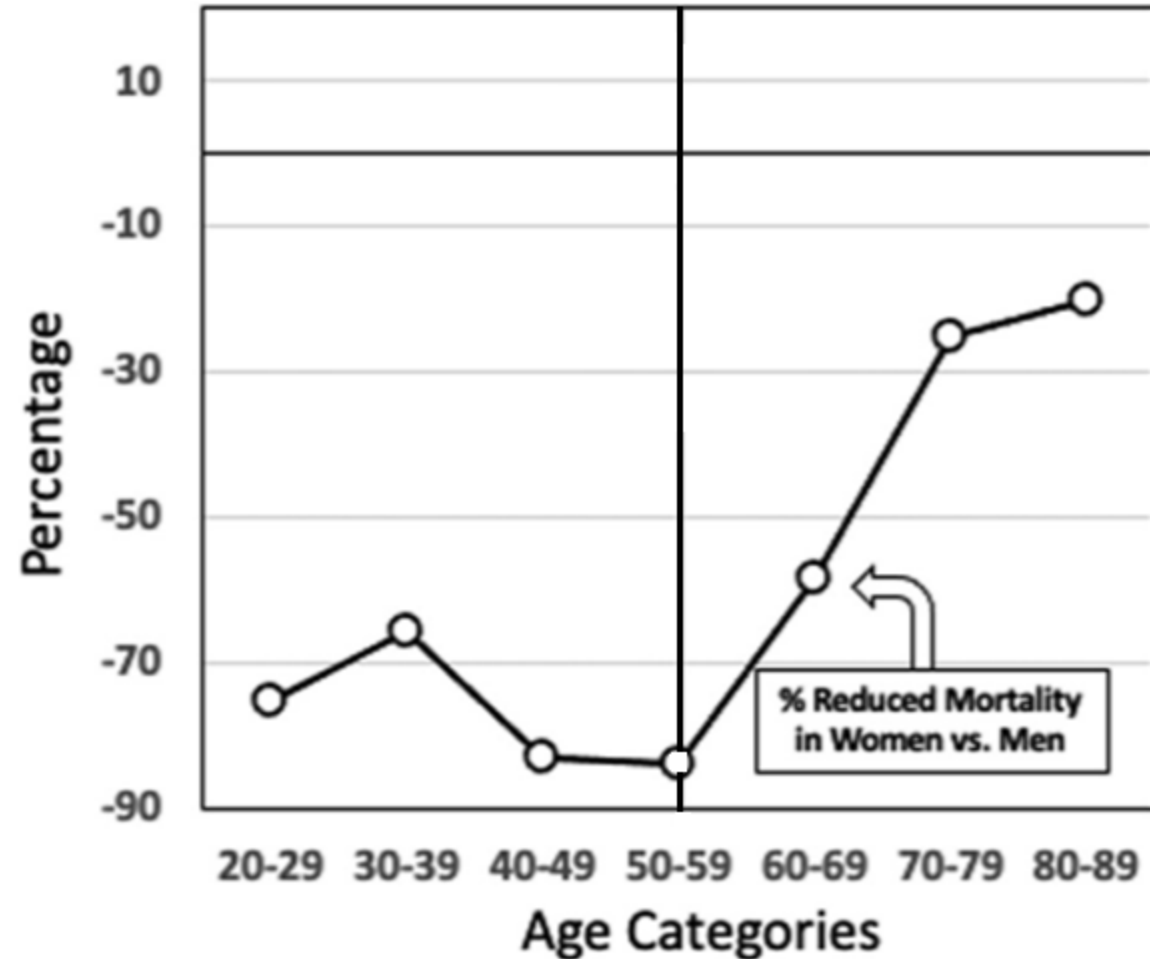


FIG. 1. Gender-related infection and death by COVID-19. Percentage variation in the prevalence of women among COVID-19-infected versus noninfected (line 0) individuals (closed circles). Percentage reduction in death rate in women versus death rate in men (line 0) (open circles). For each age group, sample size and proportion of woman (women/100 individuals) in infected/noninfected individuals was: 20 to 29 years, $n = 27,284$ (0.483/0.483); 30 to 39 years, $n = 28,366$ (0.508/0.497); 40 to 49 years, $n = 39,856$ (0.544/0.503); 50 to 59 years, $n = 51,318$ (0.529/0.511); 60 to 69 years, $n = 36,620$ (0.412/0.522); 70 to 79 years, $n = 37,016$ (0.434/0.543); 80 to 89 years, $n = 43,439$ (0.595/0.607).



COVID: Who's Getting It? Who's Dying?

- Older men get Covid more often than women

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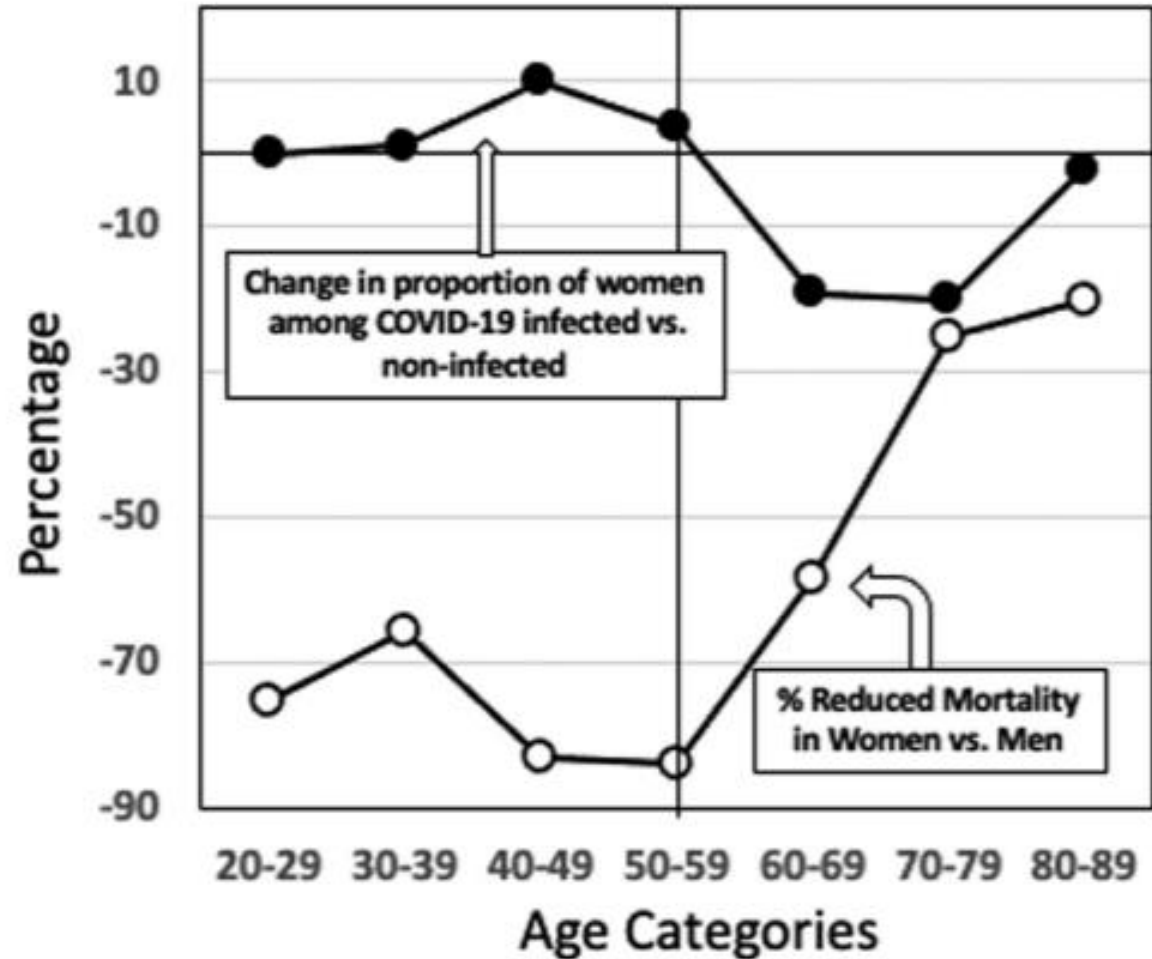


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COVID: Endocrine Health Matters!



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Children with adrenal insufficiency are 10 times more likely to die from COVID-19

SHARE



FEATURED SCIENCE FROM ENDO 2021

> **Children with adrenal insufficiency are 10 times more likely to die from COVID-19**

PRESS RELEASE

Meetings & Events

Children with adrenal insufficiency are 10 times more likely to die from COVID-19



COVID: Endocrine Health Matters!

Received: 3 November 2020

Revised: 13 November 2020

Accepted: 16 November 2020

DOI: 10.1111/apa.15673

REGULAR ARTICLE

ACTA PÆDIATRICA
NURTURING THE CHILD

WILEY

Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19

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²Department of Paediatrics, Orebro University Hospital, Orebro, Sweden

³Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK

⁴Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA

Correspondence

Jonas F. Ludvigsson, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 17177 Stockholm, Sweden.
Email: jonasludvigsson@yahoo.com

Abstract

Aim: Persistent symptoms in adults after COVID-19 are emerging and the term long COVID is increasingly appearing in the literature. However, paediatric data are scarce.

Methods: This paper contains a case report of five Swedish children and the long-term symptoms reported by their parents. It also includes a systematic literature review of the MEDLINE, EMBASE and Web of Science databases and the medRxiv/bioRxiv pre-print servers up to 2 November 2020.

Results: The five children with potential long COVID had a median age of 12 years (range 9–15) and four were girls. They had symptoms for 6–8 months after their clinical diagnoses of COVID-19. None were hospitalised at diagnosis, but one was later admitted for peri-myocarditis. All five children had fatigue, dyspnoea, heart palpitations or chest pain, and four had headaches, difficulties concentrating, muscle weakness, dizziness and sore throats. Some had improved after 6–8 months, but they all suffered from fatigue and none had fully returned to school. The systematic review identified 179 publications and 19 of these were deemed relevant and read in detail. None contained any information on long COVID in children.

Conclusion: Children may experience similar long COVID symptoms to adults and females may be more affected.



COVID-Endocrine Patterns

- **The relationship between COVID-19 and the endocrine system is bidirectional, occurring at multiple levels**
- **In the brain**
 - **Elevated LH, FSH, Prolactin**
 - **Lower TSH, ACTH, Growth Hormone**



COVID-Female Hormone Patterns

- **Women have been impacted more than men by COVID in terms of life impact, especially if they are essential workers...more of these roles are filled by women (78% of hospital jobs)**
- **Covid has brought increased childcare challenges, and the consequences of this have fallen disproportionately on women**
- **The literature doesn't describe severe impact from Covid on female reproductive hormones**
- **Lower E2 and Pg (only in SARS 2010)???**
- **Stress...Stress...Stress!!!**




COVID-Female Hormone Patterns

- **Women have more irregular cycles due to anxiety/stress due indirectly to COVID**



The impact of COVID-19-related mental health issues on menstrual cycle characteristics of female healthcare providers

Taha Takmaz¹ , Ibrahim Gundogmus², Sabri Berkem Okten³ and Anil Gunduz⁴

Abstract

Aim: To investigate the association between menstrual cycle regularity in healthcare providers and COVID-19 pandemic-related anxiety, depression, stress.

Methods: A cross-sectional study was conducted by administering online questionnaires to female healthcare workers in Turkey. Women aged 18–40 years with regular menstrual cycles for more than 1 year before the beginning of the pandemic were included in the study and they were divided into two groups according to menstrual cycle regularity during the pandemic. The questionnaires included sociodemographic characteristics, medical and reproductive history, lifestyle information of participants, COVID-19 Stress Scales (CSS), and a short version of the Depression Anxiety Stress Scale (DASS-21).

Results: A total of 952 women were included in the study, 679 had regular menstrual cycles, and 273 had irregular menstrual cycles. The prevalence of irregular menses among Turkish women healthcare workers aged 18–40 years was 28.7%. The CSS subdimensions and total scores were significantly higher in the irregular menstruation group than in women with regular menstruation ($p < 0.001$). The DASS-21 depression, anxiety, and stress subdimensions were likewise significantly higher in women with irregular menstruation ($p < 0.001$). Besides, both the univariable and the multivariable logistic regression results showed the relationship between irregular menstruation and CSS total score.

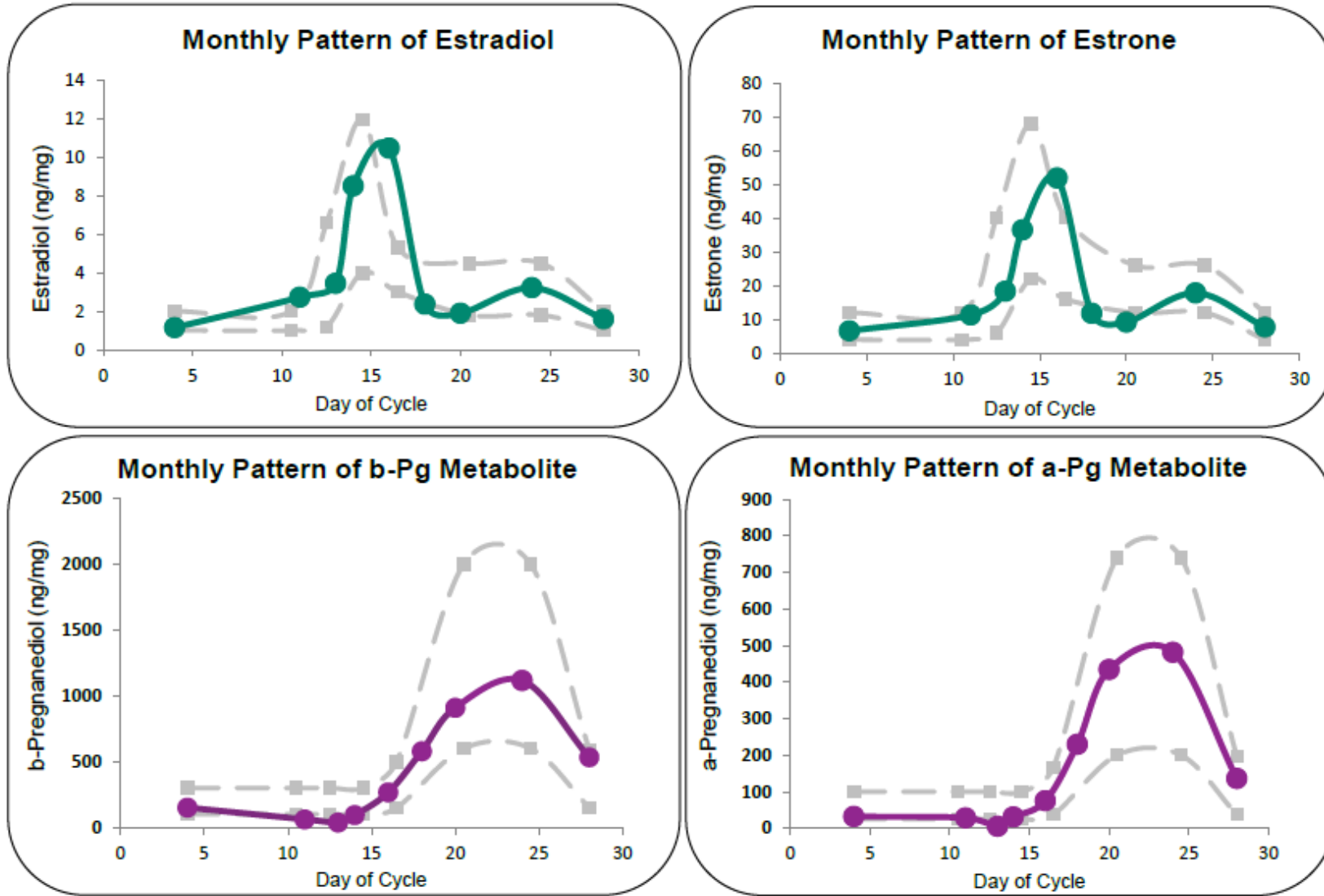
Conclusion: The current study showed the association between the COVID-19 pandemic-induced anxiety, perceived stress, depressive symptoms, and increased prevalence of menstrual cycle irregularity among healthcare providers.



COVID+ Female Hormone Patterns

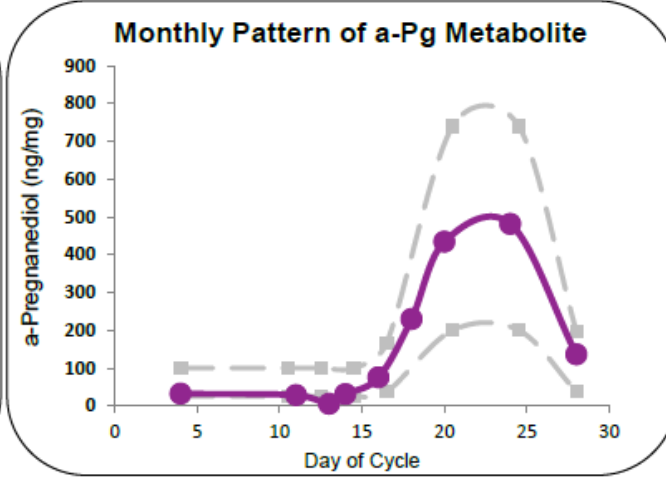
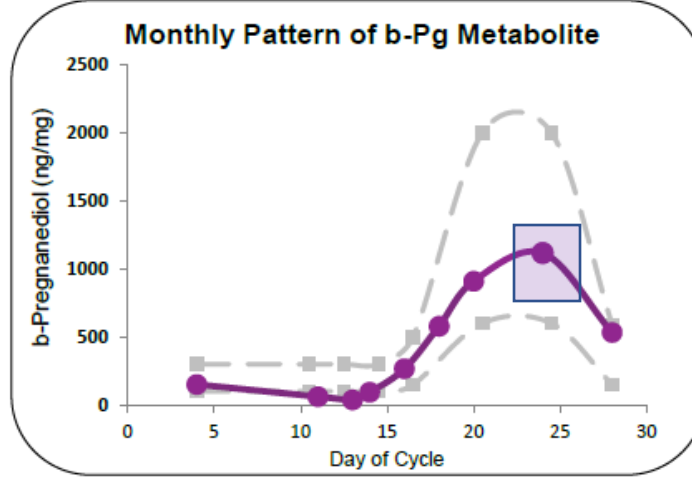
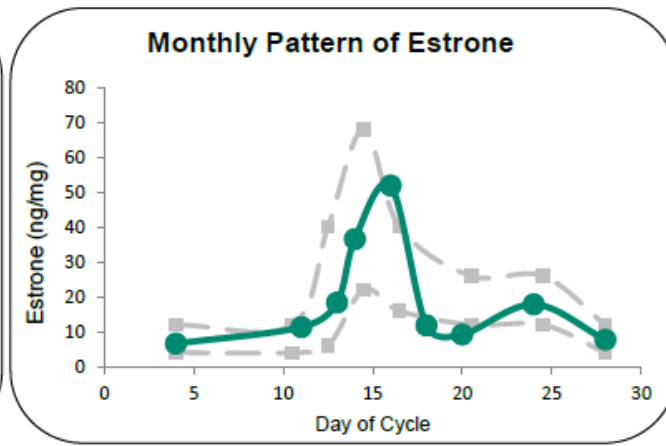
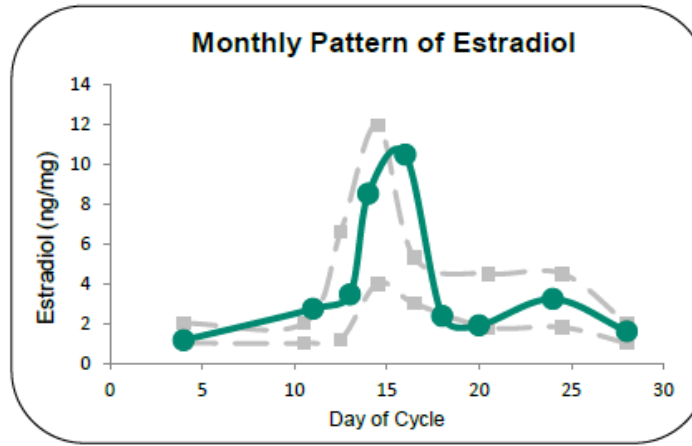


COVID+ Female Hormone Patterns



COV

erns



All values given in ng/mg creatinine

Measurement	1	2	3	4	5	6	7	8	9
Day(s) of Cycle	4	11,12	13	14,15	16,17	18,19	20,21	24	28

The days listed above were used for measurements. Two samples are used and listed for long cycles or patients without a normal cycle.

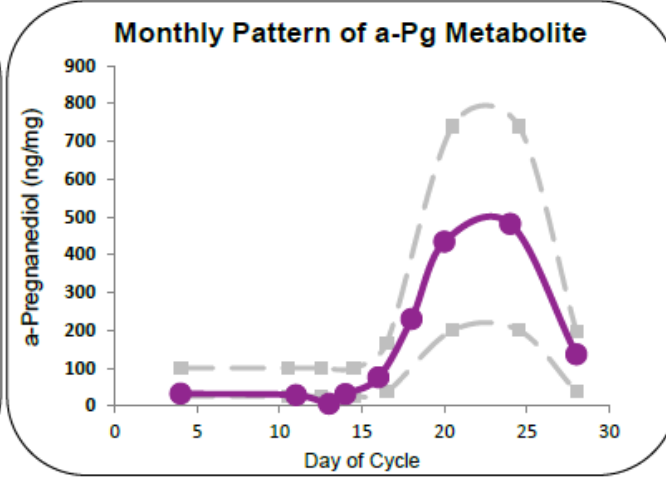
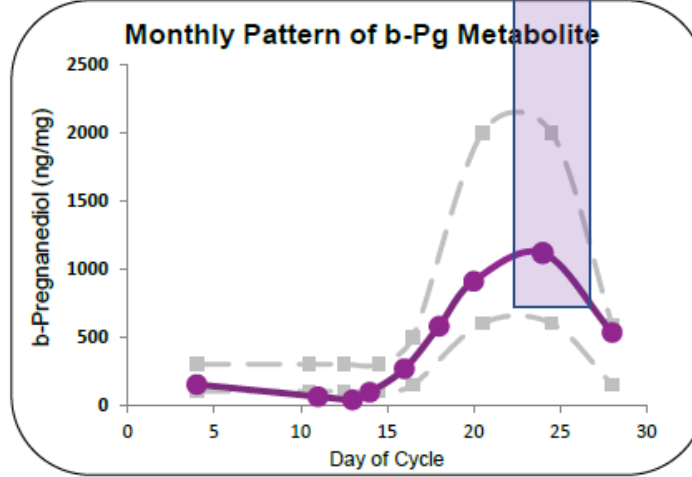
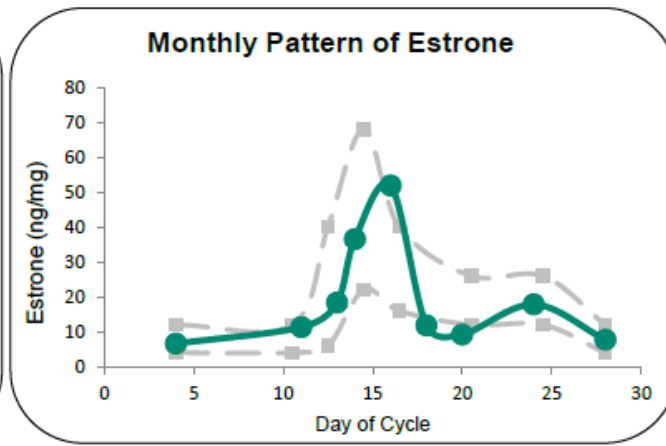
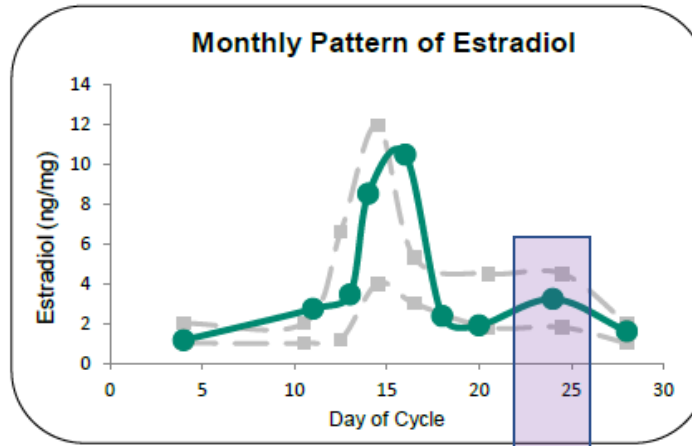
Estradiol (E2)	1.15	2.73	3.45	8.53	10.49	2.37	1.90	3.22	1.59
Estrone (E1)	6.6	11.3	18.3	36.5	51.9	11.8	9.2	17.8	7.7
a-Pregnanediol	32	28	6	31	75	229	434	481	136
b-Pregnanediol	150	62	38	94	266	579	909	1116	533
b-Pregnanediol/E2 Ratio	131	23	11	11	25	244	479	346	334
Creatinine	1.00	0.37	0.47	0.85	0.81	0.41	0.35	0.42	0.22

Sample (#8) with the highest b-Pg value (1116) is used for E and Pg metabolites for DUTCH Complete or Plus if ordered.



COV

erns



All values given in ng/mg creatinine

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Day(s) of Cycle	4	11,12	13	14,15	16,17	18,19	20,21	24	28

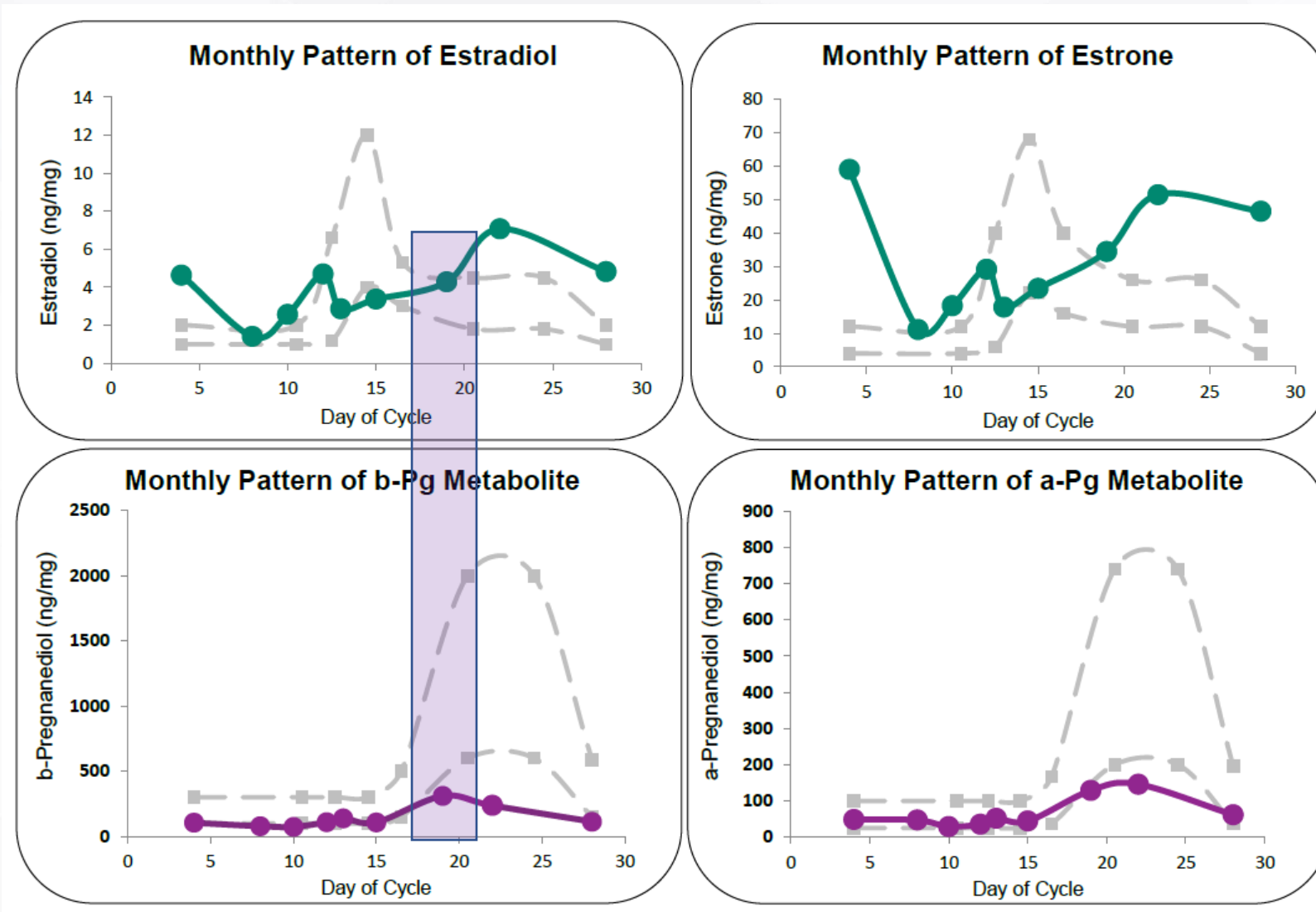
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COVID+ Female Hormone Patterns



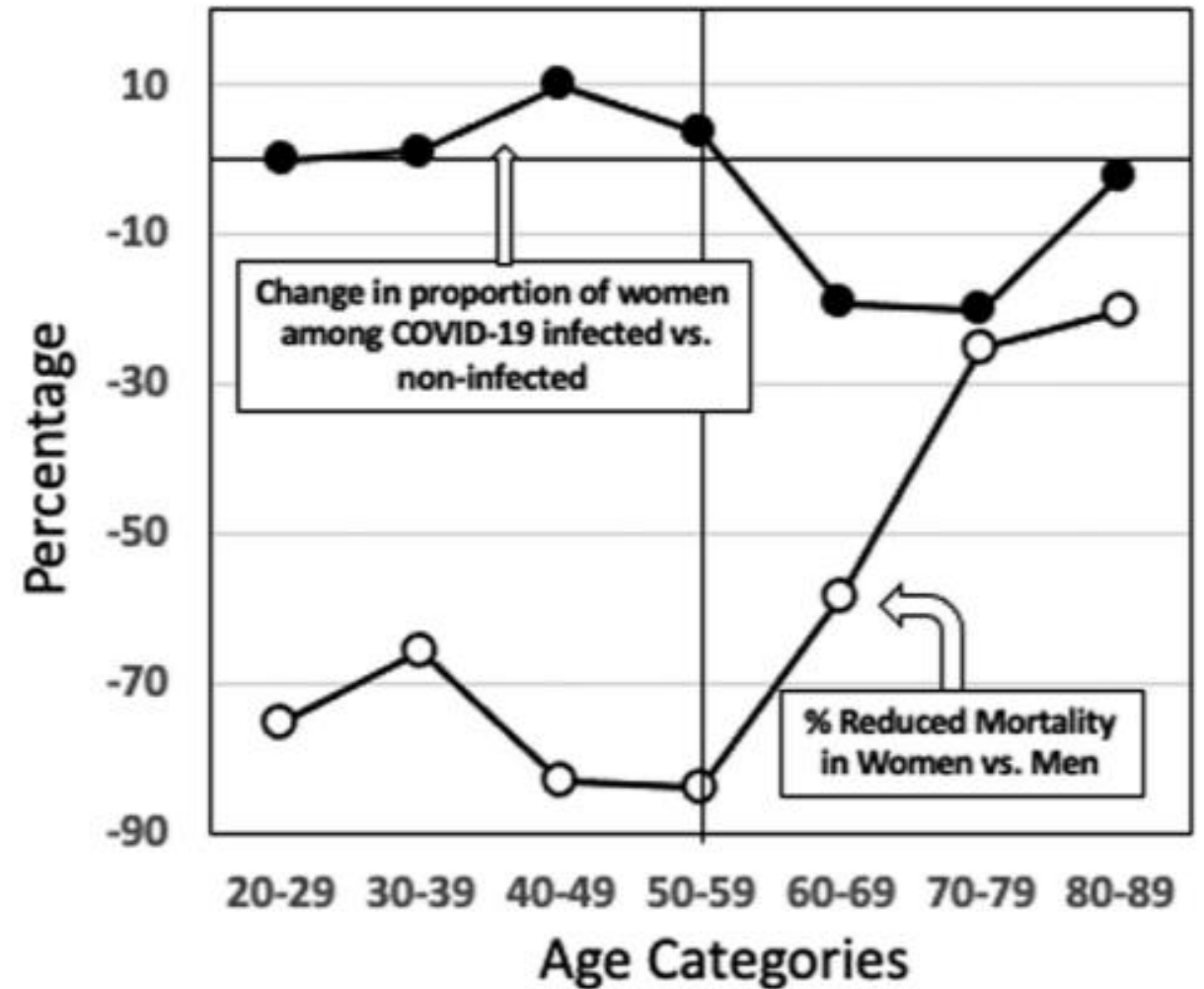
COVID-Female Hormone Patterns

- Women have more irregular cycles due to anxiety/stress due indirectly to COVID
- PCOS women potentially at higher risk of/from Covid
- Some evidence progesterone may be helpful
- Estrogen's relationship with Covid is somewhat paradoxical and complex
- E2 can act on cellular subsets of the immune system by epigenetic mechanisms resulting in modulation of lymphocyte activity and number...perhaps why females clear the virus earlier than males (ERT connection?)



- Estrogen may have a permissive role on ACE2 expression
 - Higher disease rates in young
 - Lower rates compared to men in PMP
- ACE2 may have a protective role against disease progression
 - Lower mortality for premenopausal women
 - Higher mortality rates for PMP
- No mention of HRT in this paper

CAGNACCI AND XHOLLI
Menopause, Vol. 28, No. 5, 2021



- ERT Potentially Protective
- “Women on HRT with COVID-19 had a lower likelihood of death”
- This is NOT peer-reviewed

Mortality in COVID-19 amongst women on Hormone Replacement Therapy or Combined Oral Contraception: A cohort study

Short title: COCP/HRT use in COVID-19 and mortality

Hajira Dambha-Miller¹, William Hinton², Mark Joy², Michael Feher² and Simon de Lusignan^{2,3}

ABSTRACT

Objective: To investigate the association between Hormone Replacement Therapy (HRT) or Combined Oral Contraception (COCP) use, and the likelihood of death in women with COVID-19.

Design: A cohort study

Setting: 465 general practices in England within the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) primary care database.

Population: 1,863,478 women aged over 18 years

Methods: We identified a cohort of women with COVID-19 from the computerised medical records of the RCGP RSC database. Mixed-effects logistic regression models were used to quantify the association between HRT or COCP use, and all-cause mortality among women with COVID-19 in unadjusted and adjusted models.

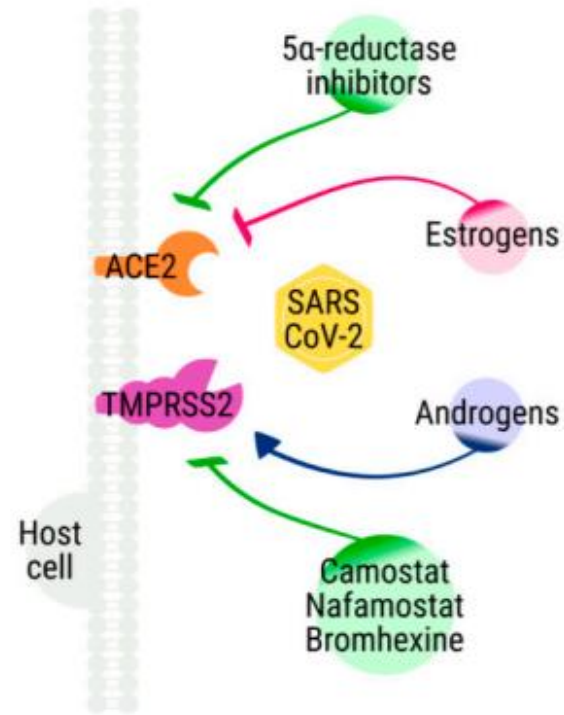
Results: There were 5451 COVID-19 cases within the cohort. HRT was associated with a significantly lower likelihood of all-cause mortality in COVID-19 (adjusted OR 0.22, 95% CI 0.05 to 0.94). There were no reported events for all-cause mortality in women prescribed COCPs. This prevented further examination of the impact of COCP.

Conclusions: Women on HRT with COVID-19 had a lower likelihood of death. Further work is needed in larger cohorts to examine the association of COCP in COVID-19. Our findings support the current hypothesis that oestrogens may contribute a protective effect against COVID-19 severity.

**COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv
(NOT Peer-reviewed)**



A: SARS-CoV-2 CELL ENTRY



B: IMMUNE MODULATION

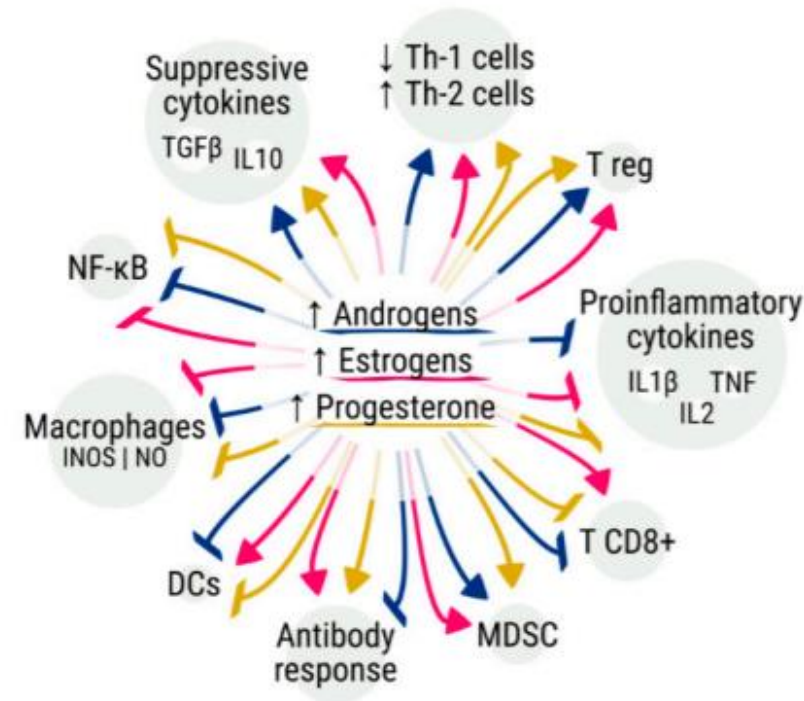


Figure 1. The role of sex hormones and hormone therapies in modulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry in host cells and immune response. **(A)** A proposed model suggests that androgens can upregulate the activity of transmembrane serine protease 2 (TMPRSS2), which is necessary for the SARS-CoV-2 spike protein priming; several TMPRSS2 inhibitors are under investigation in clinical trials. In vitro data also suggest that estrogens might downregulate the angiotensin-converting enzyme 2 (ACE2) expression, which is used by SARS-CoV-2 for host cell entry. **(B)** Androgens (blue arrows), estrogens (pink arrows), and progesterone (yellow arrows) can activate and inhibit several components of the immune response against SARS-CoV-2, affecting the clinical course and disease severity of patients with COVID-19. TGF β —transforming growth factor-beta; IL—interleukin; Th-1—T helper 1; Th-2—T helper 2; T reg—T regulatory cells; TNF—tumor necrosis factor; MDSC—myeloid-derived suppressor cells; DCs—dendritic cells; INOS—inducible nitric oxide synthase; NO—nitric oxide; NF- κ B—nuclear factor kappa-light-chain-enhancer of activated B cells.



COVID-HPA Axis Patterns

- **Direct effects on HPA – Infection of neuronal cells cause edema and necrosis**
- **Indirect effects on HPA mediated by cytokines and inflammation**
- **Inflammation damages the pituitary and hypothalamus**
- **Increased IL-1, IL-6, TNFa**
 - **Activates HPA axis and raises cortisol**
- **Cortisol increases initially with infection but Adrenal Insufficiency may be seen in critical phase**
- **Acute AI can be caused by thrombotic event at the adrenal level**
- **Oxytocin mobilizes immune defenses, limits inflammation, oxidative stress**
- **Those with Adrenal Insufficiency at higher risk of infection and higher mortality**
- **Recommended increased dose of hydrocortisone if infected with AI**
- **40% of SARS survivors hypocortisol, even if NOT on steroid treatment during...~60% recovered after 1 year**
 - **only 5% hypothyroid**
- **Low TSH, T3, T4 (also relevant to cortisol)**
- **Melatonin therapy to be considered**
 - **High safety profile, highly anti-inflammatory, anti-oxidative**



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- **Recommended increased dose of hydrocortisone if infected with AI**
- **40% of SARS survivors hypocortisol, even if NOT on steroid treatment during...~60% recovered after 1 year**
 - only 5% hypothyroid
- **Low TSH, T3, T4 (also relevant to cortisol)**
- **Melatonin therapy to be considered**
 - High safety profile, highly anti-inflammatory, anti-oxidative



COMMON MEDICATIONS MAY CAUSE ADRENAL INSUFFICIENCY

APRIL 30, 2015 BY MARK NEWMAN, MS

Everyone knows that taking corticosteroids like Prednisone can be suppressive to the adrenal glands – this is why they are usually dosed in a tapering manner in order to prevent a crash. However, new research published in the April 2015 online edition of The Journal of Clinical Endocrinology and Metabolism reports that even those who use common allergy or asthma steroid inhalers and nasal sprays are at risk for adrenal insufficiency.



Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis

Leonie H. A. Broersen, Alberto M. Pereira, Jens Otto L. Jørgensen,
and Olaf M. Dekkers

Department of Clinical Epidemiology (L.H.A.B., O.M.D.), Leiden University Medical Centre, Leiden 2300RC, The Netherlands; Department of Medicine (L.H.A.B., A.M.P., O.M.D.), Division of Endocrinology, Leiden University Medical Centre, Leiden 2300RC, The Netherlands; Department of Endocrinology (J.O.L.J., O.M.D.), Aarhus University, 8000 Aarhus C, Denmark; and Department of Clinical Epidemiology (O.M.D.), Aarhus University, 8000 Aarhus C, Denmark

Objective: We aimed to estimate pooled percentages of patients with adrenal insufficiency after treatment with corticosteroids for various conditions in a meta-analysis. Secondly, we aimed to stratify the results by route of administration, disease, treatment dose, and duration.

Methods: We searched seven electronic databases (PubMed, MEDLINE, EMBASE, COCHRANE, CENTRAL, Web of Science, and CINAHL/Academic Search Premier) in February 2014 to identify potentially relevant studies. Original articles testing adult corticosteroid users for adrenal insufficiency were eligible.

Results: We included 74 articles with a total of 3753 participants. Stratified by administration form, percentages of patients with adrenal insufficiency ranged from 4.2% for nasal administration (95% confidence interval [CI], 0.5–28.9) to 52.2% for intra-articular administration (95% CI, 40.5–63.6). Stratified by disease, percentages ranged from 6.8% for asthma with inhalation corticosteroids only (95% CI, 3.8–12.0) to 60.0% for hematological malignancies (95% CI, 38.0–78.6). The risk also varied according to dose from 2.4% (95% CI, 0.6–9.3) (low dose) to 21.5% (95% CI, 12.0–35.5) (high dose), and according to treatment duration from 1.4% (95% CI, 0.3–7.4) (<28 d) to 27.4% (95% CI, 17.7–39.8) (>1 year) in asthma patients.

Conclusions: 1) Adrenal insufficiency after discontinuation of glucocorticoid occurs frequently; 2) there is no administration form, dosing, treatment duration, or underlying disease for which adrenal insufficiency can be excluded with certainty, although higher dose and longer use give the highest risk; 3) the threshold to test corticosteroid users for adrenal insufficiency should be low in clinical practice, especially for those patients with nonspecific symptoms after cessation. (*J Clin Endocrinol Metab* 100: 2171–2180, 2015)



COVID-HPA Axis Patterns

- Direct effects on HPA – Infection of neuronal cells cause edema and necrosis
- Indirect effects on HPA mediated by cytokines and inflammation
- Inflammation damages the pituitary and hypothalamus
- Increased IL-1, IL-6, TNF α
 - Activates HPA axis and raises cortisol
- Cortisol increases initially with infection but Adrenal Insufficiency may be seen in critical phase
- Acute AI can be caused by thrombotic event at the adrenal level
- Oxytocin mobilizes immune defenses, limits inflammation, oxidative stress
- **Those with Adrenal Insufficiency at higher risk of infection and higher mortality**
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COVID Impact on Cortisol Production

Reviews in Endocrine and Metabolic Disorders (2020) 21:495–507
<https://doi.org/10.1007/s11154-020-09569-2>

Endocrine and metabolic aspects of the COVID-19 pandemic

Mónica Marazuela¹ · Andrea Giustina² · Manuel Puig-Domingo³

6 The pituitary and COVID-19

Evidence of altered pituitary function in SARS was first reported by Leow et al. [64]. Sixty-one survivors of the SARS outbreak were evaluated after recovery: 40% had evidence of central mild hypocortisolism and 5% also had central hypothyroidism [64]. Edema and neuronal degeneration along with

9/61 → 7.4M

Bangladesh Journal of Medical Science, Vol : 20
Special Issue on Covid19, 2021

Covid 19 and Adrenal Insufficiency

After recovery, these patients complained of malaise, fatigue, weakness, orthostatic dizziness, lassitude, apathy, anorexia, anxiety, and depression. Three months following recovery, it was noted that 39.3% of patients developed hypocortisolism, 83.3% of which had central hypocortisolism as shown by low adrenocorticotrophic hormone (ACTH) levels¹¹⁰.

Interestingly, most of these individuals did not receive any systemic glucocorticoids during treatment for SARS; thus, the possibility of HPA axis suppression by exogenous corticosteroid use was ruled out. The hypocortisolism was resolved in 62.5% of patients within a year with an average duration of 5.9±3.1 month since the condition developed was transient.

Generally, stress-induction, testosterone, and cortisol increase following adrenocorticotrophic hormone (ACTH) release (Viau, 2002). But SARS-CoV, like the influenza virus, acquires one of the primary immunoinvasive strategies subverting the host cortisol-stress-response. Reportedly, SARS-CoV bears amino acids mimicking host ACTH molecules which in turn stimulate host antibody production capable of destroying the actual circulating ACTH molecules (Wheatland, 2004). As previously mentioned, nucleotide sequences of SARS-CoV-2 are similar to SARS-CoV (Ren et al., 2020), thus it may recruit similar strategies of molecular mimicry and thereby suppress stress-induced increase in ACTH level (Xu et al., 2020).

WHY/HOW??

HUMAN FERTILITY
<https://doi.org/10.1080/14647273.2020.1867902>

COVID-19 and hypogonadism: secondary immune responses rule-over endocrine mechanisms

Pallav Sengupta^a  and Sulagna Dutta^b 

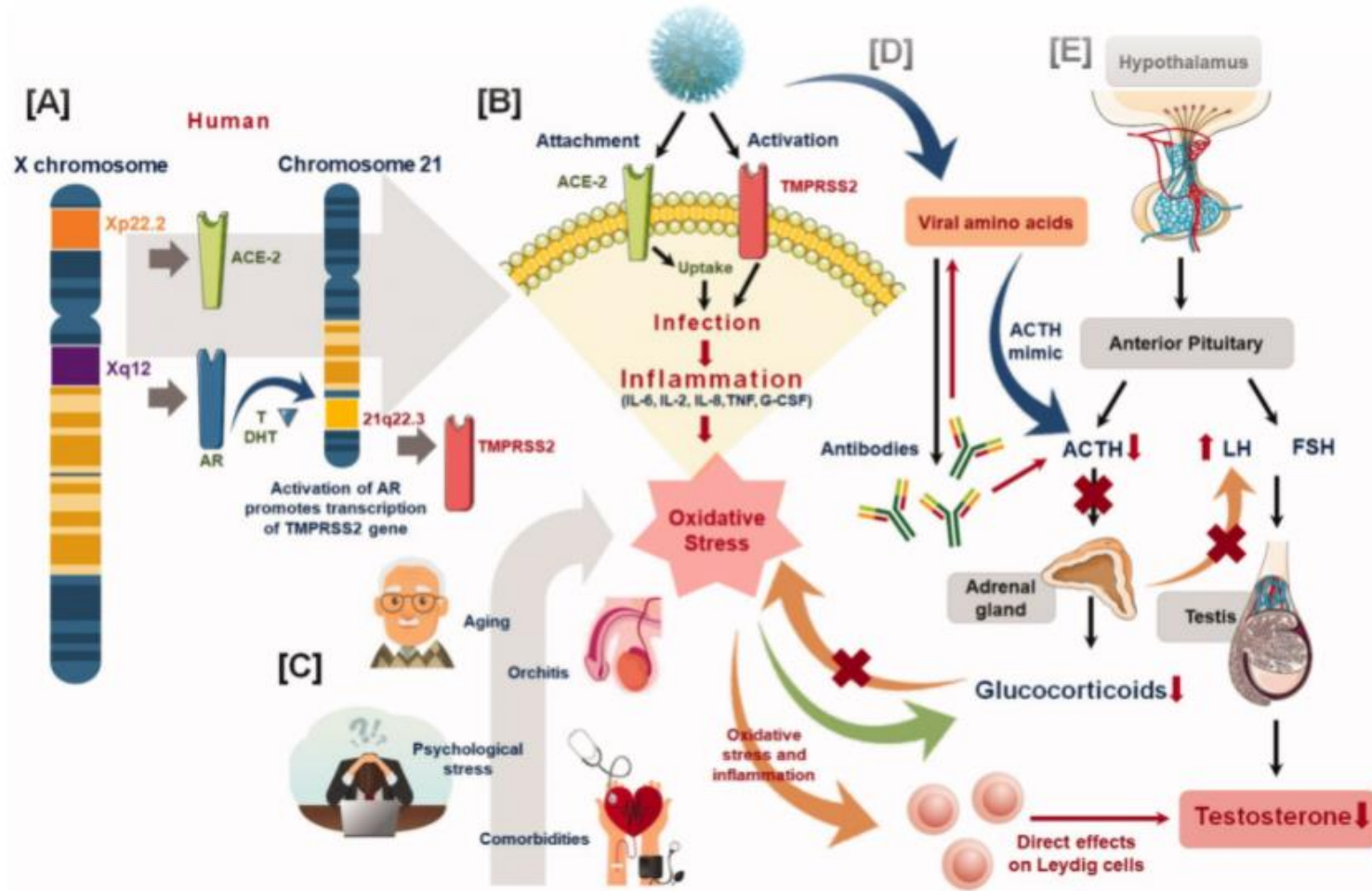
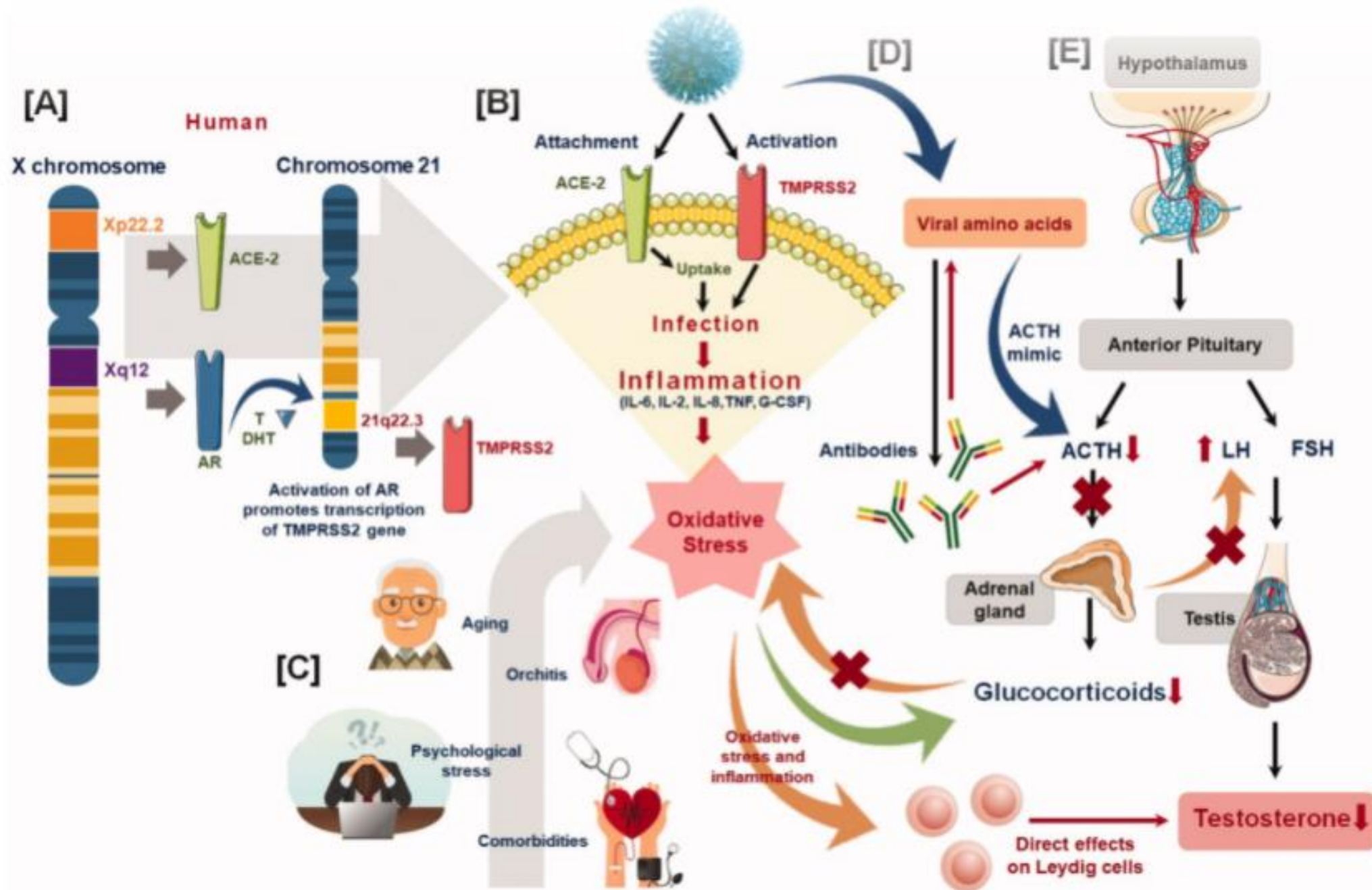


Figure 1. Possible mechanisms of SARS-CoV-2 infection mediated testosterone depletion. (A) androgen receptor and ACE2 are located in chromosome-X, while androgen receptor activation is needed to trigger *TMPRSS2* gene transcription, aiding SARS-CoV-2 entry into host cells; (B) SARS-CoV-2 infection triggers inflammatory responses and oxidative stress-mediated disruptions of Leydig cell functions; (C) Advanced age, psychological, and other co-morbidities associated with COVID-19 may also lead to oxidative stress; (D) Viral amino acids may mimic ACTH molecules and stimulate production of antibodies against host ACTH, thereby reducing glucocorticoid levels and suppressing host response to combat stress; (E) Hypothalamic–pituitary–testicular (HPT) axis may not be affected by SARS-CoV-2 infection, thus due to low testosterone level, LH level remains high in COVID-19 patients. ACE2: angiotensin-converting enzyme 2; AR: androgen receptor; T: testosterone; DHT: dihydrotestosterone; *TMPRSS2*: transmembrane protease serine-2; IL: interleukin; TNF: tumour necrosis factor; G-CSF: granulocyte colony-stimulating factor; ACTH: adrenocorticotrophic hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone.



COVID-Androgen Patterns

- **Men, more infections, worse outcomes**
- **In the brain**
 - **Elevated LH**
- **Testicular production**
 - **ACE-2 receptors and cellular serine protease (TMPRSS2) help SARS-CoV-2 enter the cells and these are abundant in testes, which may act as viral reservoir**
 - **Though LH is elevated, testosterone levels are lower (primary hypogonadism)**
- **Less COVID for those on prostate cancer related anti-androgens**
 - **TMPRSS2 inhibitors may help COVID**
- **Androgens have an immunosuppressive effect**
- **Men hospitalized have more androgenic alopecia**



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Low T good?

JAAD Journal of the American Academy of Dermatology

RESEARCH LETTER | VOLUME 83, ISSUE 2, P680-682, AUGUST 01, 2020

Androgenetic alopecia present in the majority of patients hospitalized with COVID-19: The “Gabrin sign”

Carlos Gustavo Wambier, MD, PhD   • Sergio Vaño-Galván, MD, PhD • John McCoy, PhD • ...



MP28-11

USE OF 5A-REDUCTASE INHIBITORS IS ASSOCIATED WITH LOWER RISK OF INFECTION WITH SARS-COV-2

Madison Lyon, Jianbo Li, Alex Milinovich, Nima Sharifi, Eric A. Klein, Cleveland, OH*

CONCLUSIONS: Men without prostate cancer taking a 5aRI are at lower risk for community acquired COVID-19 infection.

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INTRODUCTION AND OBJECTIVE: The TMPRSS protein serves as a host co-receptor for the SARS-CoV-2 virus that causes COVID-19 and is present in both prostate and lung tissue. This protein is known to be androgen regulated in the prostate, however, there is conflicting data on whether it is also androgen regulated in the lung, an important site for COVID-19 infection. Two randomized controlled trials have shown 5a-reductase inhibitors (5aRI) reduced the severity of COVID-19 symptoms in infected men, and reduced the likelihood of hospitalization. In the present study, we assessed the effect of 5aRI use on risk of community acquired COVID-19 infection.

METHODS: All men without prostate cancer included in an institutional prospective registry of all patients tested for SARS-CoV-2 between March 8, 2020 and February 15, 2021 were included. Patients in the 5ARI cohort were matched at a 1:1 ratio to those not on 5ARI based on demographics and comorbidities that are known to increase the risk of infection. Exact matching was performed on race, diabetes, hypertension, coronary artery disease and immune suppressive disease. The main outcome measures were the effect of 5aRI use on the rate of SARS-Cov-2 positivity and disease severity as measured by hospitalization, ICU admission, and death.

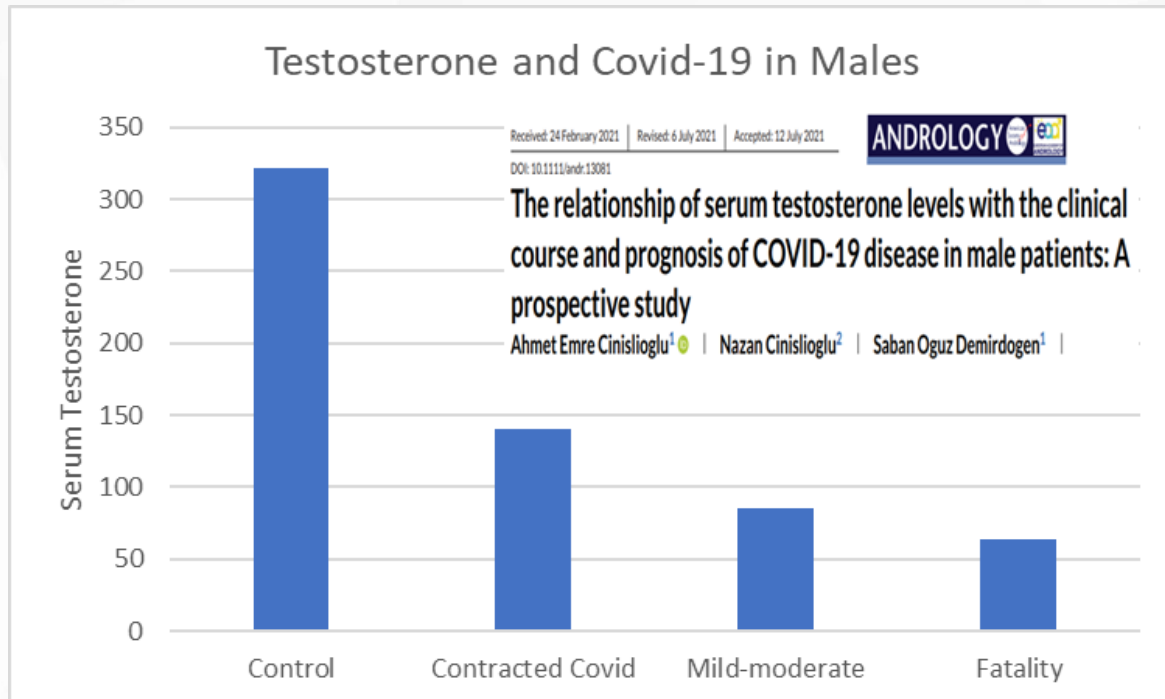
RESULTS: 60,474 males without prostate cancer diagnosis were initially selected, of which 1,079 were on 5ARI (1.8%). The matched cohorts included 1,075 on 5ARI and 1,075 non-5ARI, aged 21 to 99 years (Fig. 1). Of all the demographics and risk factors none were significantly different between the 5ARI groups in the matched cohorts. Risk for SARS-CoV-2 was significantly lower in the 5ARI group (OR 0.82, 95% CI 0.69-0.97, $p=0.024$, Table). Multivariable logistic regression analysis based on the entire data before matching reached the same conclusion.

CONCLUSIONS: Men without prostate cancer taking a 5aRI are at lower risk for community acquired COVID-19 infection.



COVID-Androgen Patterns

- Testosterone has anti-inflammatory properties
- Men with lower T do not do well with Covid (chicken or the egg?)
- Men have lower T ~10 weeks post-Covid (but LH values were low in this study)
- Do men on TRT do better???



Received: 11 February 2021 | Revised: 14 May 2021 | Accepted: 25 May 2021

DOI: 10.1111/cen.14537

Male pituitary–gonadal axis dysfunction in post-acute COVID-19 syndrome—Prevalence and associated factors: A Mediterranean case series

Oscar Moreno-Perez^{1,2} | Esperanza Merino³ | Rocio Alfayate⁴ |
Maria Eugenia Torregrosa⁴ | Mariano Andres^{2,5} |
Jose-Manuel Leon-Ramirez⁶ | Vicente Boix^{2,3} | Joan Gil⁶ |
Antonio Pico^{1,2} | COVID19-ALC Research group

Results: One hundred and forty-three patients were evaluated at a median (inter-quartile range) of 77 days (72–83) after disease onset; 72% of them recovered from severe pneumonia. LT was detected in 41 patients (28.7%; 95% CI: 21.8–36.5).

Conclusions: Prevalence of male LT and impaired fertility potential in COVID-19 survivors is high in the medium term. Traditional risk factors and severity markers for COVID-19 could be predictive. (~10 Weeks Post-Covid-19)

Does TRT help?

- **Data is promising but not conclusive**
- **Be careful with conclusions from small studies or those with subjects unlike your patients.**

Okpechi SC., et al Global sex disparity of COVID-19

depend on TMPRSS2 for viral activation and cell entry [63-65]. These studies have a unifying conclusion that the upregulation of TMPRSS2 by androgen receptor activity could be the reason for the increased male predominance in deaths from COVID-19. Surprisingly, we have come to realize that this is not the universally accepted belief in the research field, many researchers maintain differing opinions.

A recent report has evidence that testosterone supplementation can reduce COVID-19 cytokine storm effect; thereby, suppressing SARS-CoV-2 induced inflammation [46]. In SARS-CoV-2 pneumonia patients, lower total testosterone (TT) was found in patients transferred to the ICU or deceased in the respiratory intensive care units (RICU) compared to patients transferred to internal medicine units or maintained in the RICU in stable condition [62]. Another group conducted

COVID-Androgen Patterns

Role of testosterone in COVID-19 patients – A double-edged sword?

Aneela N. Hussain^a, Fazal Hussain^{b,*}, Shahrukh K. Hashmi^c

A B S T R A C T

COVID-19 affects males twice as frequently as females with significantly increased severity and mortality. Current data suggest a direct correlation between the lower level of serum testosterone, inflammatory cytokines, disease severity, and poor clinical outcomes among male patients with COVID-19. The gradual decline in total and free testosterone levels has a direct correlation with serious pulmonary complications requiring advanced care (ICU, ventilators, ECMO, etc.). SARS-CoV-2 utilizes Angiotensin-Converting Enzyme II (ACE2) for entry in the host cell, and Transmembrane Protease, Serine 2 (TMPRSS2) to prime spike protein of SARS-CoV-2. Testosterone induces ACE-2 expression, a critical pulmonary protective enzyme. Low testosterone levels in males have a direct correlation with the high probability of ICU admission and the worse disease outcome (ARDS, duration of ICU stay, mortality). On the contrary, however, high testosterone levels can lead to thrombosis which is also one of the fatal manifestations in COVID-19 patients. A critical evaluation of the serum testosterone and its relevance to COVID-19 is warranted to re-evaluate strategies to effectively triage, prioritize, and manage high-risk patients for ICU admission, survival outcomes, targeted solutions, and operational algorithms.



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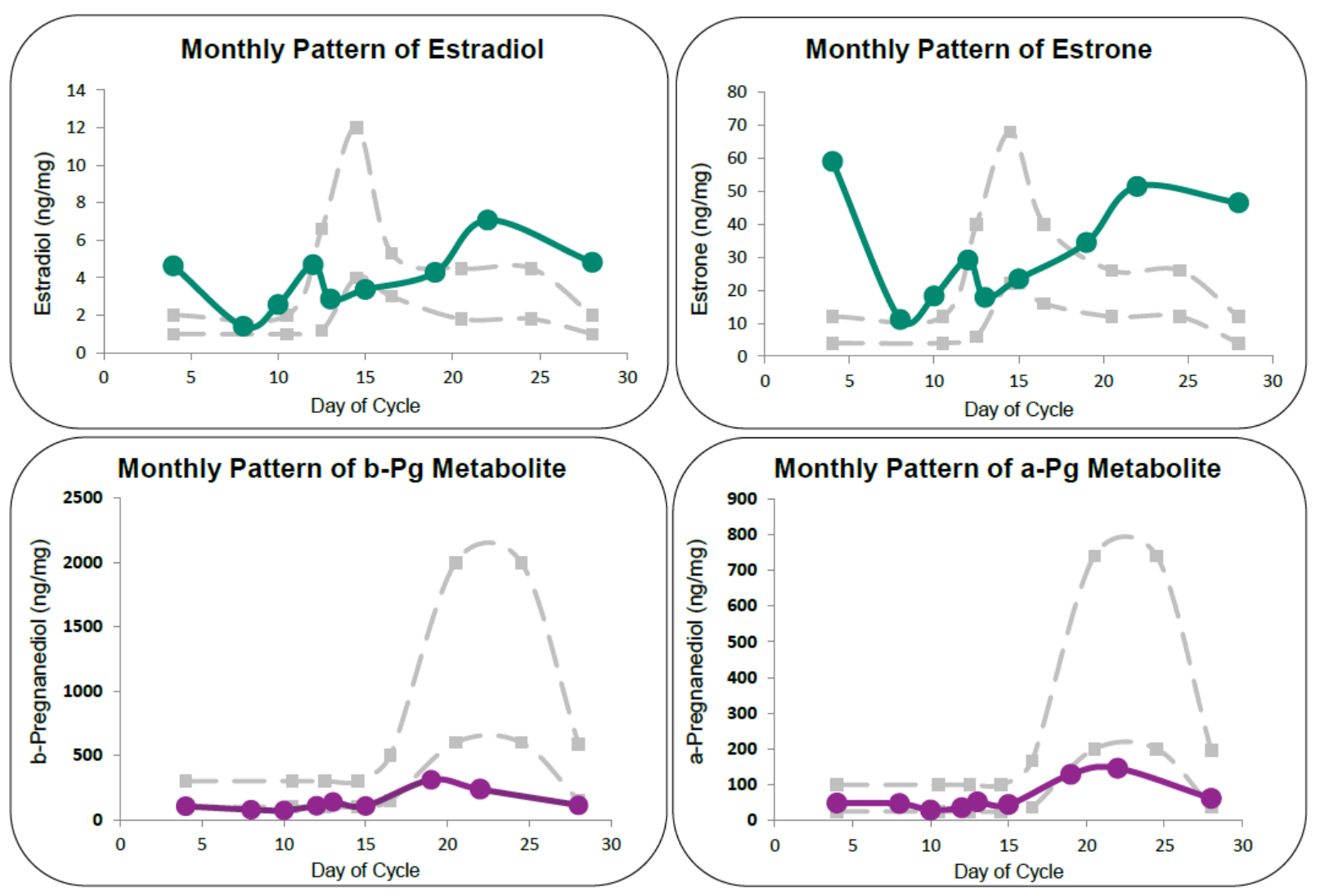
Covid-19 Recovered Case Studies

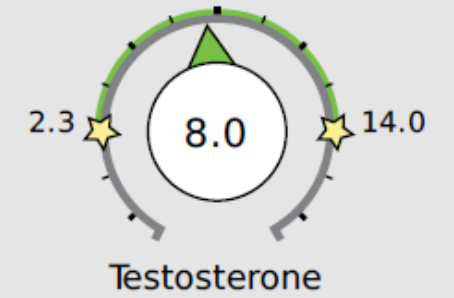


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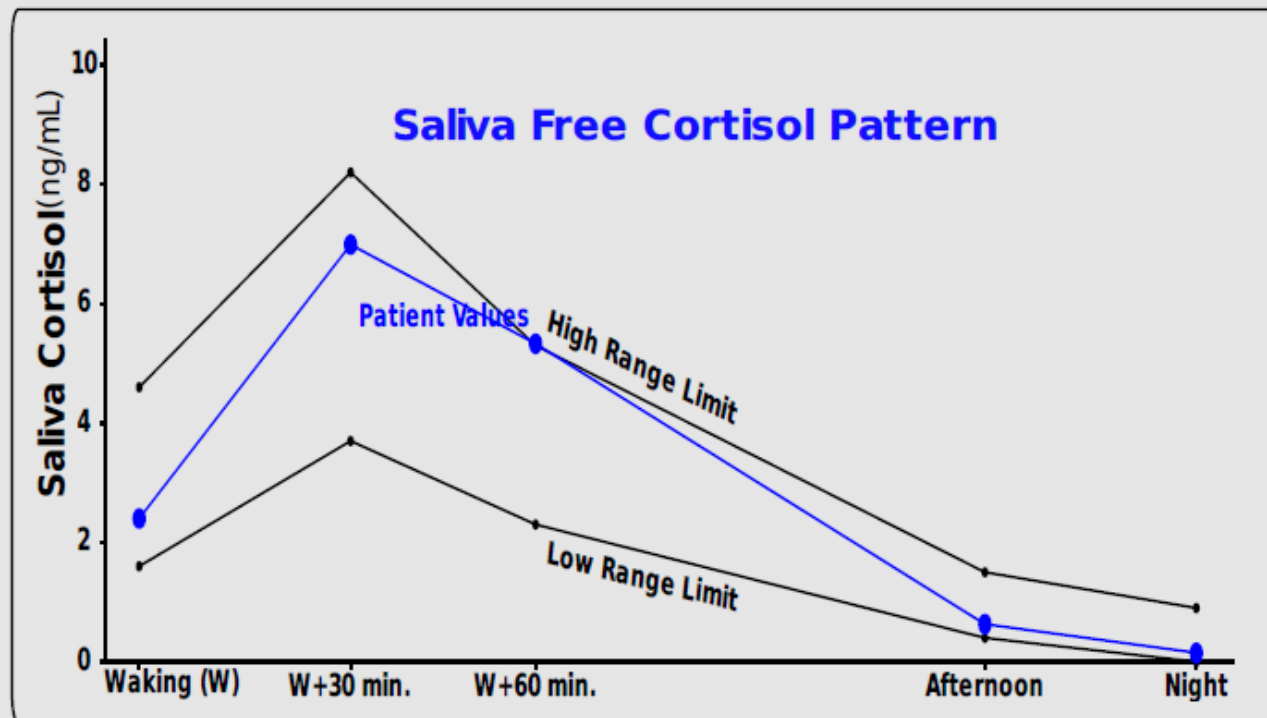


COVID+ Female Hormone Patterns



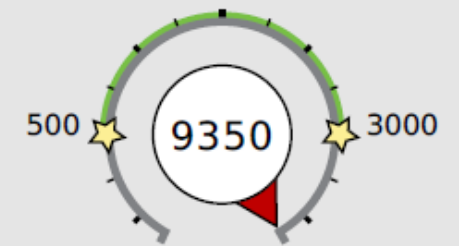


Adrenal Hormones See pages 4 and 5 for a more complete breakdown of adrenal hormones

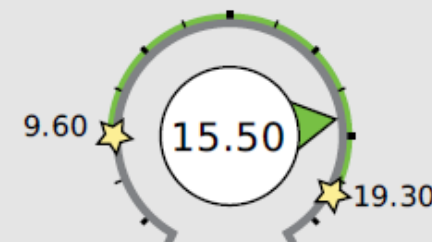


Total DHEA Production

Age	Range
20-39	1300-3000
40-59	750-2000
>60	500-1200



Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)



Saliva Cortisol Total
(Sum of 5 values)






cortisol
metabolism



Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

Research Article:

COVID-19 Patients Suffer From DHEA-S Sufficiency

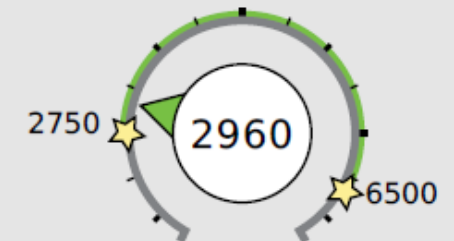
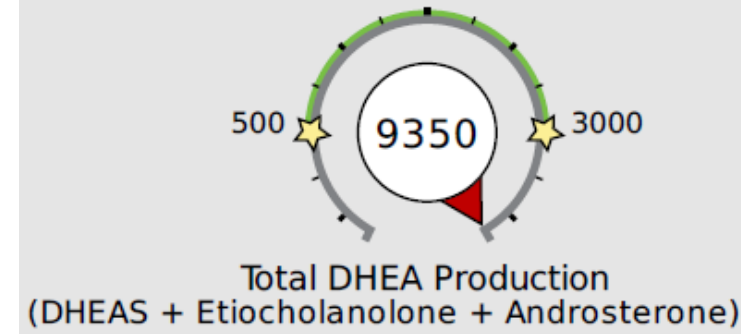
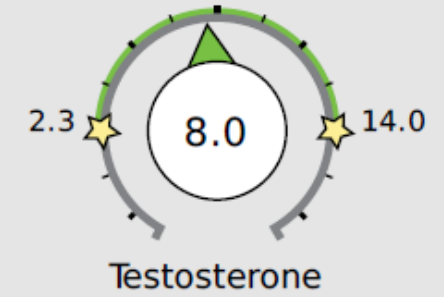
Mohammad Reza Vaez Mahdavi¹ , Sussan Kaboudanian Ardestani², Arezou Rezaei³ , Saeed Mohammadi⁴, Maryam Rajabnia Chenary⁵, Behnaz Gharegozlou⁶ , Mohammad Mehdi Naghizadeh^{7,8} , Tooba Ghazanfari^{7*} 

ABSTRACT

Background: The nervous, endocrine, and immune systems contribute to the response and dynamic adaption to various stresses. Activation of the hypothalamic-pituitary-adrenal axis has been demonstrated in various active critical illnesses. Novel Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is a disease with age and gender disparities.

Results: While the increase in cortisol level was not significant in COVID-19 patients, the DHEA-S level and DHEA-S/cortisol ratio significantly decreased in the patients with the increase in severity of the disease.

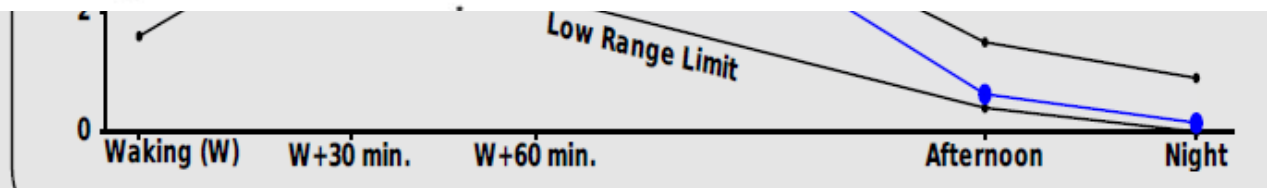
Conclusion: We proposed that the supplementation of DHEA, the precursor of both androgens and steroids, may ameliorate adverse outcomes of COVID-19 disease and improve COVID-19 patients' ability to survive.



Saliva Cortisol Total
(Sum of 5 values)

cortisol
metabolism

Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

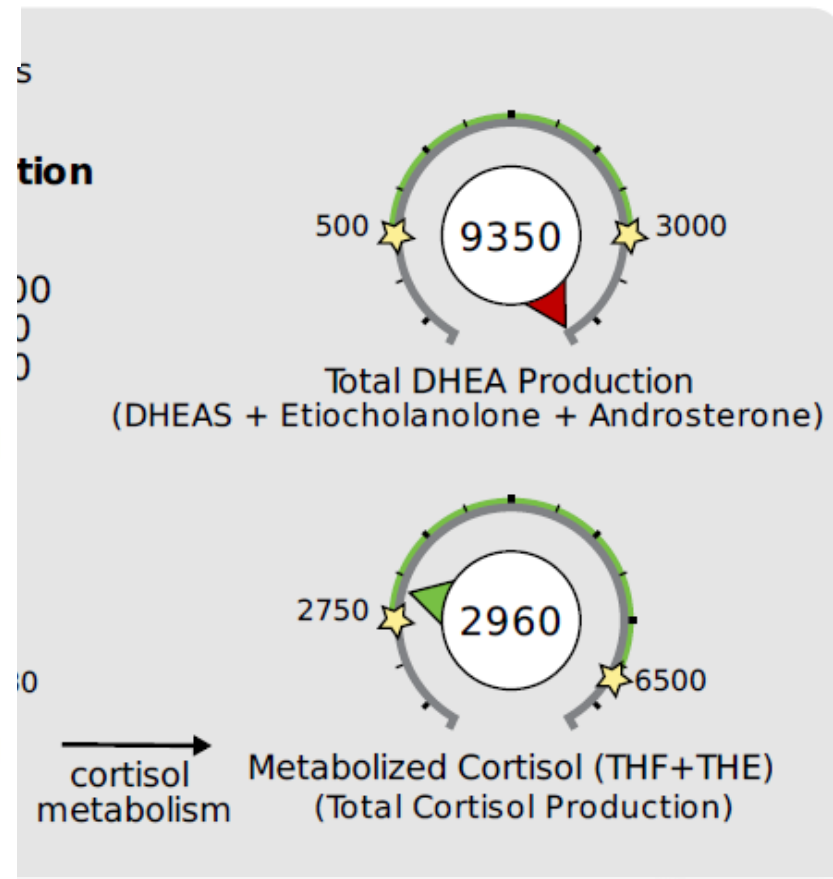
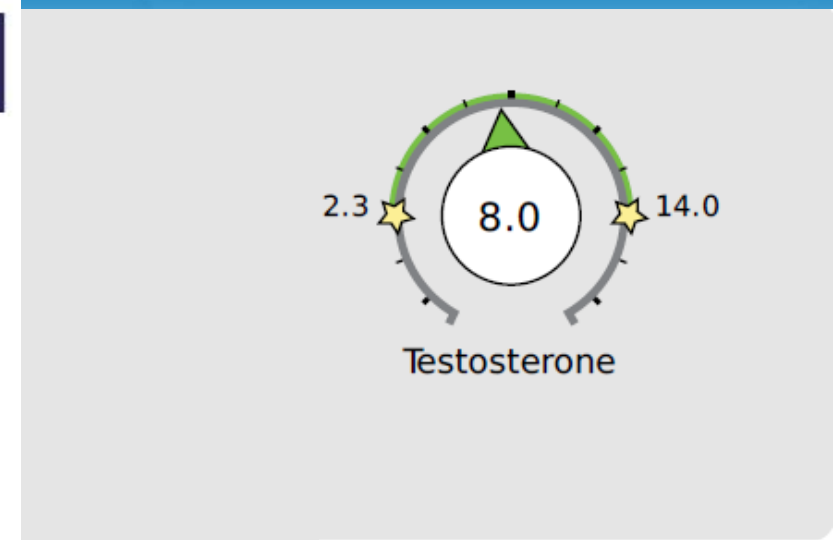


REVIEW

Alert to US physicians: DHEA, widely used as an OTC androgen supplement, may exacerbate COVID-19

Abstract

Androgens play a fundamental role in the morbidity and mortality of COVID-19, inducing both the ACE-2 receptor to which SARS-CoV-2 binds to gain entry into the cell, and TMPRSS22, the transmembrane protease that primes the viral spike protein for efficient infection. The United States stands alone among developed nations in permitting one androgen, oral DHEA, to be freely available OTC and online as a 'dietary supplement'. DHEA is widely used by males in the US to offset the age-related decline in circulating androgens. This fact may contribute to the disparate statistics of COVID-19 morbidity and mortality in this country. In regulatory antithesis, every other developed nation regulates DHEA as a controlled substance. **DHEA is an extremely potent inhibitor of glucose-6-phosphate dehydrogenase (G6PD), with uniquely unstable uncompetitive inhibition kinetics. This has particular relevance to COVID-19 because G6PD-deficient human cells have been demonstrated to be exceptionally sensitive to infection by human coronavirus.** Because DHEA is lipophilic and freely passes into cells, oral DHEA bypasses the normal controls regulating androgen biology and uncompetitive G6PD inhibition.





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[\[HTML\] Alert to US physicians: DHEA, widely used as an OTC androgen supplement, may exacerbate COVID-19](#)

J Nyce - Endocrine-Related Cancer, 2021 - erc.bioscientifica.com

Androgens play a fundamental role in the morbidity and mortality of COVID-19, inducing both the ACE-2 receptor to which SARS-CoV-2 binds to gain entry into the cell, and TMPRSS22, the transmembrane protease that primes the viral spike protein for efficient ...

[RE: Low DHEA causal in Covid-19 is further Antagonized by Testosterone](#)

JM Howard - 2021 - science.sciencemag.org

It is my hypothesis that Covid-19 infection and subsequent pathology are caused by low dehydroepiandrosterone (DHEA)(© Copyright 2020, James Michael Howard, Fayetteville, Arkansas). It is already known that DHEA provides protection from pathogenic viruses. In this ...

[RE: Covid-19 Vulnerability is Caused by Low DHEA and High Testosterone](#)

JM Howard - 2021 - science.sciencemag.org

I suggest the basis of Monod, et al., is low dehydroepiandrosterone (DHEA) during high testosterone levels. DHEA naturally begins to decline around age 20-25 while testosterone remains high at this time. It is my hypothesis that Covid-19 infection and subsequent ...

[COVID-19 Patients Suffer From DHEA-S Sufficiency](#)

SK Ardestani, M Vaezmahdavi... - ..., 2021 - research.shahed.ac.ir

Background: The nervous, endocrine, and immune systems contribute to the response and dynamic adaption to various stresses. Activation of the hypothalamic-pituitary-adrenal axis has been demonstrated in various active critical illnesses. Novel Coronavirus Disease 2019 ...

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MR Vaez Mahdavi... - ..., 2020 - immunoreg.shahed.ac.ir

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[\[PDF\] Does dehydroepiandrosterone sulfate have a role in COVID-19 prognosis and treatment?](#)

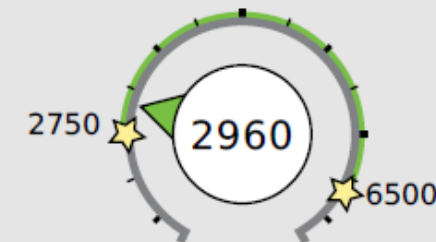
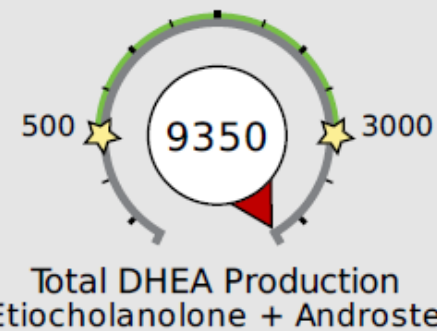
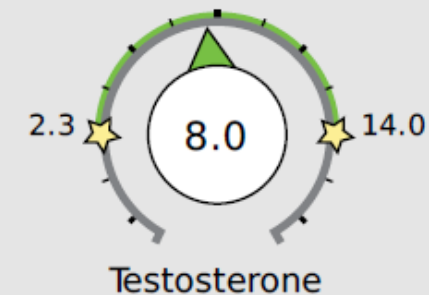
S Tomo, M Banerjee, P Sharma, M Garg - Endocrine Regulations, 2021 - sciendo.com

... Key words: COVID-19, hypothalamic-pituitary-adrenal axis, DHEA, DHEAS, cortisol ... 1997). The evidence from other viral diseases justifies the attempts that the therapeutic efficacy of DHEA and its analogs in COVID-19 disease may be taken into assess. Conclusion ...

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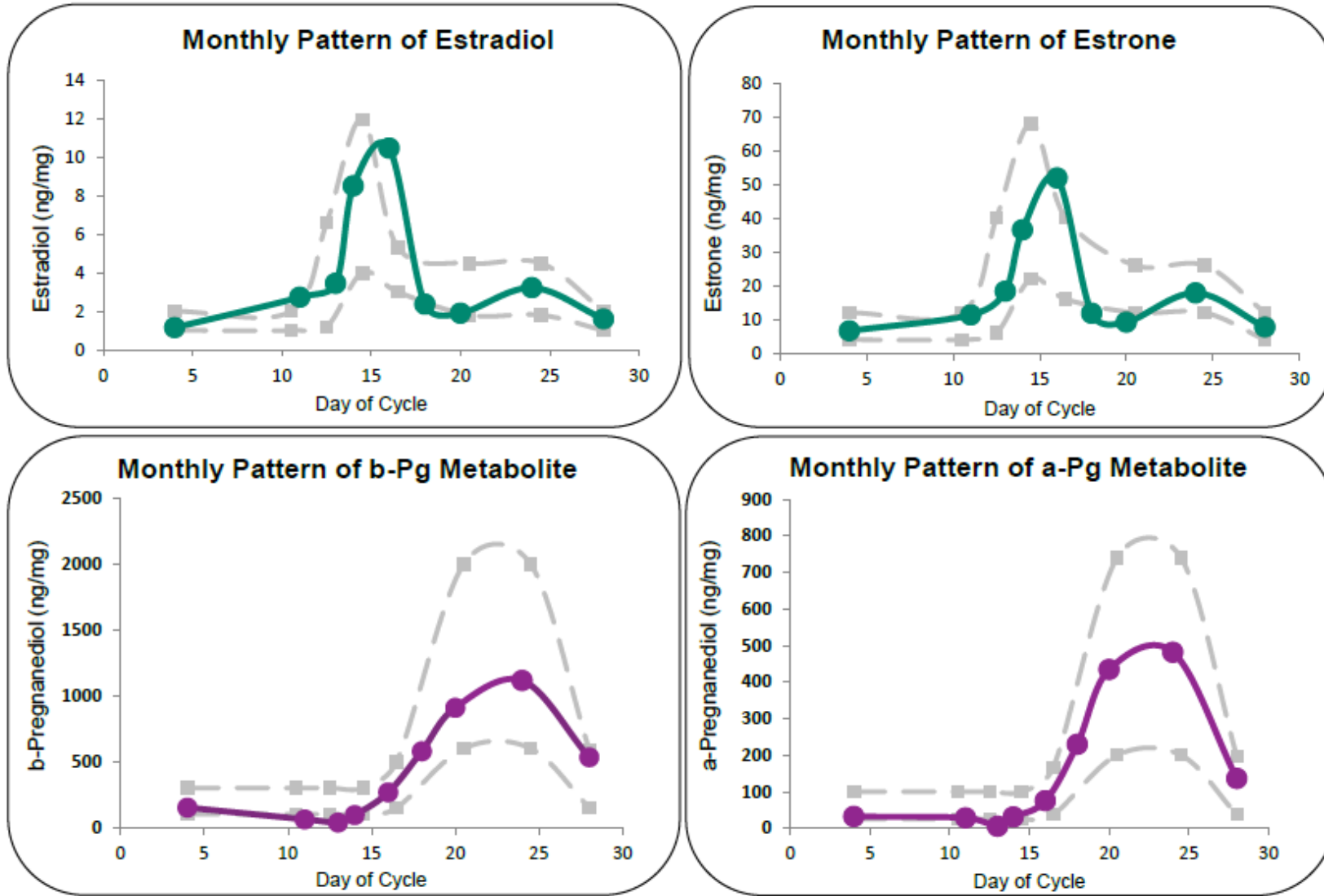
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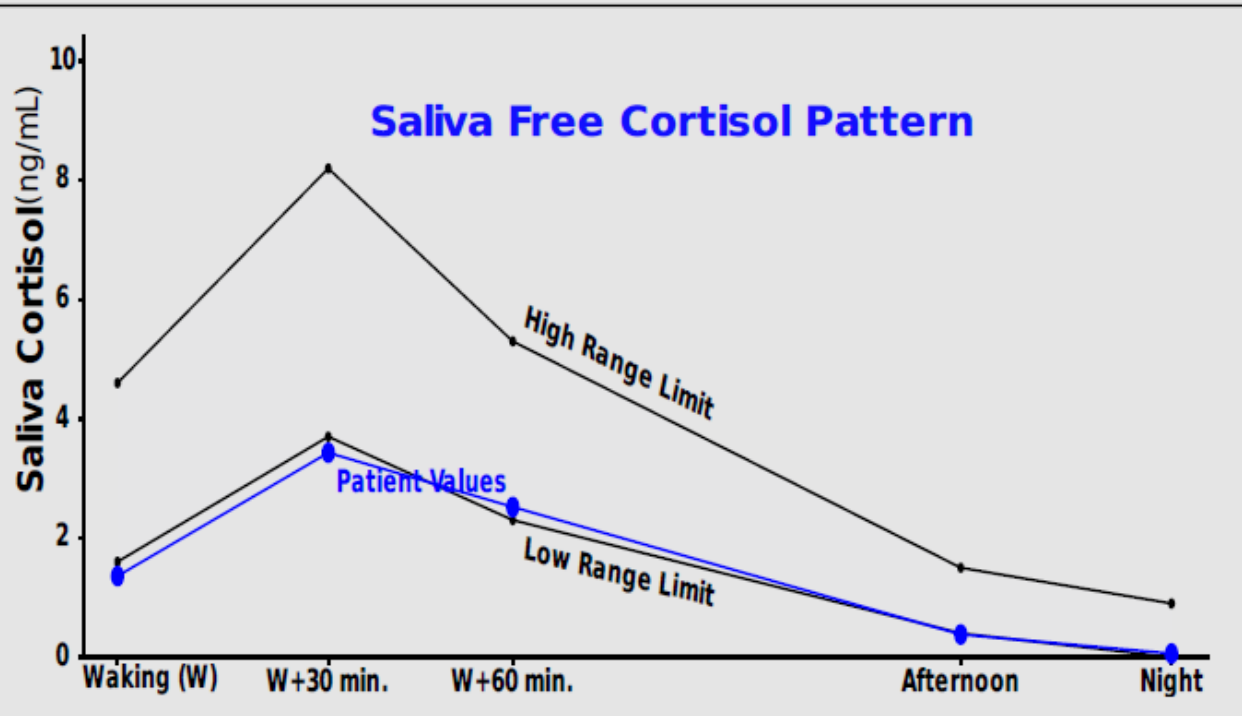
→ Cortisol Metabolism

COVID+ Female Hormone Patterns



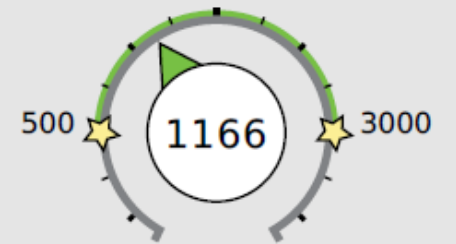
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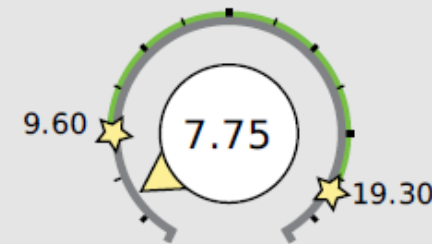


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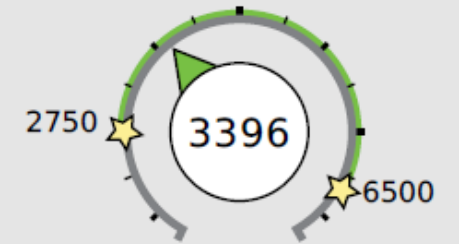


Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)



Saliva Cortisol Total
(Sum of 5 values)

cortisol
metabolism



Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

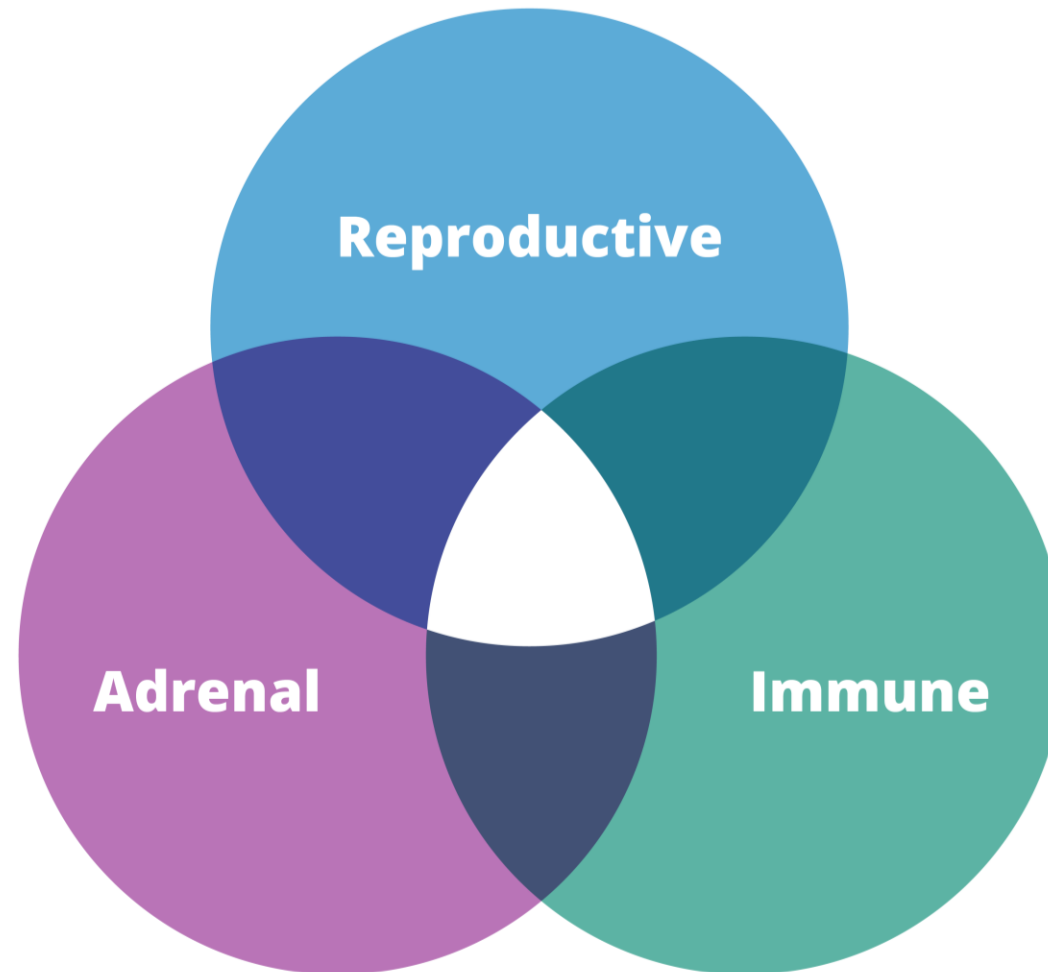


COVID-Endocrine Patterns

- **Proper hormonal function is helpful for successfully surviving COVID-19**
- **Patients with insufficient cortisol production may be at higher risk, especially Addison's or full suppression.**
- **E2 & testosterone play important, but complex roles.**
- **Discontinuing HRT doesn't seem justified, except DHEA.**
- **Long Covid patient endocrine patterns are still emerging, but hormone dysfunction definitely plays a role.**
 - **Low cortisol, testosterone (male) of special interest.**



Complex Problems Need Comprehensive Solutions



Dried Urine

- Estrogen (production)
- Estrogen (metabolism)
- Estrogen (methylation)
- Testosterone (production)
- Testosterone (metabolism)
- DHEA (production)
- DHEA (metabolism)
- Progesterone (production)
- Cortisol (free pattern)
- Cortisol (production)
- Cortisol (metabolism)
- B6, B12, Glut. deficiency
- Neurotransmitter balance
- Oxidative stress
- Melatonin (production)

DUTCH Complete

Saliva

- Cortisol (free pattern)
- Cortisol (CAR)

DUTCH Plus

DUTCH Cycle Map





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