“Estrogens: Harnessing the power of nature against COVID-19 and emerging viral infections”

Virtual Expert Panel

28 May 2021, 15:00-16:30 CEST / 09.00-10.30 EDT

Meeting Summary

Disclaimer

The views expressed are those of the speakers and may not necessarily reflect the opinion of Mithra. Mithra does not guarantee the accuracy or reliability of the information provided.

Background

Since early in the COVID-19 pandemic, it has been recognized that women are less likely to die of the disease than men, despite being more likely to become infected. This male predominance of deaths is consistent with that seen in the prior coronavirus epidemics, SARS-CoV and MERS-CoV. Estrogens are known to modulate the immune system and there is increasing evidence that estrogens, both those produced by the body and those given in the form of oral contraceptives or menopausal hormone therapy, may be playing an important role in improving the outcomes of COVID-19 infection.

Mithra, a Belgian biotech company, has recently completed the enrolment of male and female patients into an international Phase 2 clinical trial of estetrol (E4, a novel oral estrogen) for the treatment of COVID-19. This randomized, controlled, double-blinded clinical trial is expected to be the first prospective clinical trial of an estrogen to report results in COVID-19.

While these results are awaited, Mithra brought together an international panel of experts in endocrinology, women’s health, infectious disease, and intensive care medicine, to present and discuss the rationale and preclinical and observational clinical data for estrogens in COVID-19 and other viral diseases, the different types of estrogens and how they are currently being studied in COVID-19, how COVID-19 is currently managed, and how an oral estrogen might play a role in therapy of both men and women with COVID-19.

Expert Panel Participants

Co-Chairs

- **Prof. Jean-Louis Vincent**, MD, PhD, Professor of Intensive Care Medicine, Université Libre de Bruxelles; Dept. of Intensive Care, Erasme University Hospital, Brussels, Belgium
- **Dr. Graham Dixon**, PhD, Chief Scientific Officer, Mithra, Liège, Belgium

Panellists

- **Prof. Franck Mauvais-Jarvis,** MD, PhD, Professor of Medicine and Pharmacology, Section of Endocrinology & Metabolism, Tulane University School of Medicine; Director, Tulane Center of Excellence in Sex-Based Biology & Medicine, New Orleans, USA
- **Dr. Louise Newson,** BSc(Hons), MBChB(Hons), MRCP, FRCGP, General Practitioner & Menopause Specialist, Newson Health, Stratford-upon-Avon, UK
- **Prof. Jean-Michel Foidart,** MD, PhD, Permanent Secretary, Belgian Royal Academy of Medicine, former Head of Gynecology & Obstetrics, University of Liège, Belgium
- **Prof. Krzysztof Simon, MD, PhD,** Head of the Division of Infectious Diseases and Hepatology, Wrocław Medical University, Poland

Introductions & Meeting Objectives

Dr. Graham Dixon, Liège, Belgium

Dr. Dixon welcomed the panellists, and outlined the meeting objectives and agenda:

Topic	Speaker
Introductions & meeting objectives	Graham Dixon
Rationale for the use of estrogens to mitigate COVID-19	Franck Mauvais-Jarvis
Evidence summary for MHT/COC reducing mortality and disease severity	Louise Newson
Relevant features of different estrogens and current clinical research for COVID-19	Jean-Michel Foidart
Standard of care of COVID-19 and how an oral estrogen could fit	Krzysztof Simon
Moderated discussion	Jean-Louis Vincent
Summary, conclusions, next steps	Graham Dixon

Rationale & pharmacological evidence for potential use of estrogens in COVID-19

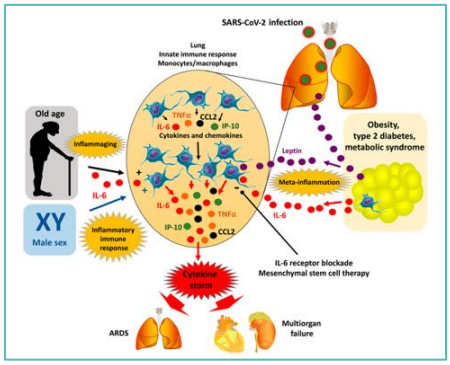
Prof. Franck Mauvais-Jarvis, New Orleans, USA

Summary

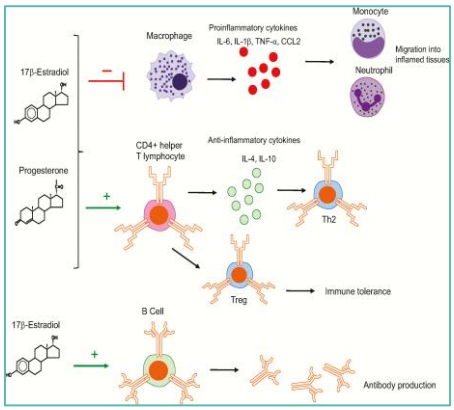
- Solid rationale and preclinical evidence for potential use of sex hormones against COVID-19
- Some evidence of protective effect against other viral infections
- Protection seems to be driven especially by modulation of innate and adaptive immunity and anti-inflammatory effects
- The role of estrogens and progesterone should be clarified by the results of ongoing clinical trials

Key points

- Aging, male sex, obesity, and metabolic inflammation create the perfect storm for COVID-19 [1]



- Relative female protection is seen in COVID-19 case fatality rates (CFR) worldwide [2]
  - On average, male CFR is 1.7x higher than female CFR
  - Consistent with the pattern observed in SARS-CoV and MERS-CoV
- Estradiol and progesterone have anti-inflammatory and immunomodulatory actions [3]



- Females predominate in the prevalence of autoimmune disorders [4]

- Sex-based differences in susceptibility to SARS-CoV infection may have an endocrine basis [5]
    - Estrogens protect female mice from SARS-CoV-1 induced cytokine storm, reversed by ovariectomy or ER antagonists
- Estrogens also protect mice from influenza virus pathogenesis and severe disease [6, 7]
- Prof. Mauvais-Jarvis is conducting a randomized control trial of acute (5-day) intramuscular estradiol and progesterone therapy in hospitalized adults to reduce COVID-19 severity [8]

Evidence summary for MHT/COC reducing COVID mortality and disease severity

Dr Louise Newson, Stratford-upon-Avon, UK

Summary

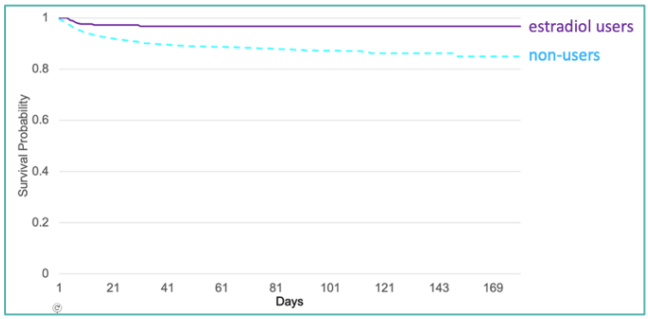
- The 3 studies presented had varying results and several limitations, but there are signals that estrogens may be reducing COVID-19 mortality and morbidity in both pre- and post-menopausal women
- More research in this area is really needed

Key points

- Menopausal Hormone Therapy (MHT)
    - Menopause affects all women
    - Estrogen has beneficial effects on multiple organs
    - For the majority of women, the benefits of MHT outweigh any risks
    - There is no maximum length of time for taking MHT
- Estrogens may have protective effects
    - MHT improves symptoms and reduces the risk of multiple conditions [9]
    - International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) hospital admission data in England, Scotland and Wales showed that women taking MHT were less likely to die
- **Study 1:** Estrogen and COVID-19 symptoms: associations in women from the COVID symptom study (pre-print) [10]
    - Studied possible link between predicted COVID-19 and menopausal status; combined oral contraceptive pill (COC); menopausal hormone therapy (MHT)
    - Self-reported information on COVID Symptom Study App; severity of disease based on hospital attendance or respiratory support
    - 44,268 post-menopausal women compared with pre-menopausal; 17,798 women taking MHT vs. those not; 64,253 COC-users vs. non-users
    - Being pre-menopausal was found to be protective of predicted COVID-19
    - **Oral contraception was associated with a significantly lower rates of predicted COVID-19, symptoms, and hospitalization**
    - MHT use was positively associated with COVID-19 symptoms but there was lack of data on type, route and duration of MHT
- **Study 2**: Evidence for treatment with estradiol for women with SARS-CoV-2 infection [11]

- Cohort study in 17 countries, 37,086 women with COVID-19
  - 18,892 women aged 15-49 with or without oral contraceptives use
  - 16,891 women aged 50+ with or without MHT use
- Retrospective analysis of a real-world database; primary outcome was death
- **Fatality risk for women > 50 years receiving estradiol therapy was reduced by more than 50% compared with non-users**
- The risk reduction for fatality from 6.6% (non-user) to 2.3% (user) was statistically significant ($p < 0.0001$)
- Effect in women using COC was smaller

Survival probability of age 50+ women, estradiol users compared with non-users



- **Study 3**: Mortality in COVID-19 amongst women on Hormone Replacement Therapy or Combined Oral Contraception: A cohort study (pre-print) [12]
  - 1,863,478 women >18 years, of whom 5,451 with COVID-19; 12.2% died
  - Age, co-morbidities, extreme BMI and immunosuppressants all significantly associated with an increased likelihood of death in women with COVID-19
  - **MHT users had significantly lower likelihood of all-cause mortality in COVID-19** (adjusted odds ratio 0.22, p= 0.041)
  - In COC users, no reported deaths (so impact of COC could not be assessed)

Summary of the 3 studies

Study	MHT use	COC use
Costeira, Spector, Newson et al	Higher predicted COVID-19 rate but hospitalization rate not significantly different	Significantly lower predicted COVID-19 likelihood, symptom frequency, hospitalization rate
Seeland et al	>50% reduction in fatality risk	Smaller reduction
Dambha-Miller et al	Significantly lower likelihood of all-cause mortality in COVID-19	Unable to assess (no reported deaths in COC users)

Relevant features of different estrogens and current clinical research for COVID-19

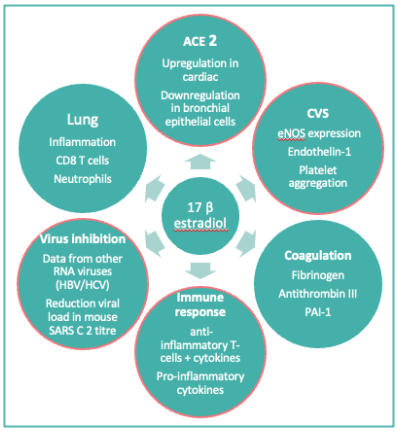
Prof. Jean-Michel Foidart, Liège, Belgium

Summary

- Estrogens have multiple effects that may be relevant for treating COVID-19
- E4 is a **N**ative **E**strogen with **S**elective action in **T**issues, a unique mode of action, a low risk for drug-drug interactions, no active metabolites, and minimal impact on liver proteins and hemostasis
- Mithra's Phase 2 clinical trial of E4 in COVID-19 is expected to report results soon

Key points

- Male sex is a risk factor for SARS-CoV-2 infection, and COVID-19 morbidity and mortality [13]
- Estrogens are antiviral in general, but the effects on ACE-2, CVS, virus inhibition and immune response are key in SARS CoV-2 infection [1, 14, 15]



  - Natural human estrogens: estrone (E1); 17β-estradiol (E2); estriol (E3); E4 [16] [data on file Mithra]
  - E4
    - The early life native estrogen
    - **N**ative **E**strogen with **S**elective action in **T**issues
    - **Unique mode of action**, acting differently depending on the tissue
      - ❖ Antagonist on the membrane ERα
        - ▪ Neutral effect on the liver; low impact on normal and malignant breast
      - ❖ Agonist on the nuclear ERα
        - ▪ Beneficial estrogenic activity on vagina, endometrium, bone, CVS
    - **Low risk for drug-drug interactions**
      - ❖ Is not metabolized by cytochrome P450 (unlike other estrogens)
    - **No active metabolites**
    - **Minimal impact on liver proteins**
    - **Minimal impact on hemostasis**

- The choice of estrogen modulates the effects of COCs on hemostasis parameters
  - E4/drospirenone has lower or similar hemostatic changes vs. ethinylestradiol/ levonorgestrel; less pronounced changes than ethinylestradiol/ drospirenone [17]
  - Important because SARS-CoV-2 induces hemostatic abnormalities
- **E4 Phase 2 trial in SARS-CoV-2 infection** has **completed enrolment**
  - A Randomized, Double-blind, Placebo-controlled Trial to Determine the Safety and Efficacy of E4 for the Treatment of Patients with Confirmed SARS-COV-2 Infection [18]
  - 162 male and post-menopausal female patients, hospitalized with COVID-19
  - Primary efficacy endpoint: % of patients recovered at Day 28
  - Expected to be the first prospective study of estrogens in COVID-19 to report

Ongoing estrogen trials: Mithra is first to complete!

Title	Location	EudraCT No.	No. of patients	Protocol	Phase	Recruitment	Treatment	Start
Estrogen patch for COVID-19 symptoms	Stony Brook Univ, NY, USA	NCT04359329	110	Open	2	Yes	E2 patch 100 µg/d for 7 days	04/2020
Estrogen therapy in non-severe COVID-19 patients	Mexico	NCT04539626	60	Open	N/A	Yes	Weekly EVRA patch (norelgestromin 6 mg / EE 0.60 mg during 21 days	10/2020
Estetrol for the treatment of patients with confirmed SARS-CoV-2 infection (Mithra trial)	**Belgium, Poland, Russia**	**NCT04801836**	**162**	**Randomized, double-blind**	**2**	**Completed**	**E4 15 mg/d for 21 days**	**11/2020**
Estrogen treatment for COVID-19 symptoms	Hamad Medical Doha, Qatar + India	NCT04853069	2000	Open, randomized	2	Not yet	Estrogel E2 3 mg/d for 10 days	05/2021
Estradiol and progesterone in hospitalized COVID-19 patients	Tulane Univ, LA, USA	NCT04865029	120	Randomized, double-blind	2	Not yet	E2 cypionate 5 mg injection at admission Progesterone oral 200 mg/d for 5 days	05/2021

E2: estradiol | E4: estetrol | EE: ethinyl estradiol

Standard of care of COVID-19 and how an oral estrogen could fit

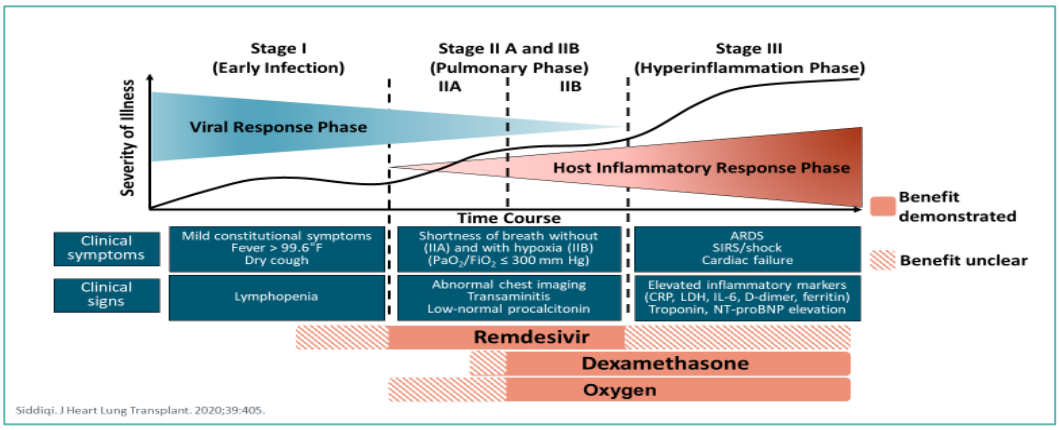
Prof. Krzysztof Simon, Wrocław, Poland

Summary

- Estrogens, as broadly acting agents, would have potential (if clinical trial data were supportive):
  - At different disease stages, in home as well as hospital settings
  - In combination with other agents
  - Irrespective of COVID-19 variants
- E4, as an oral estrogen with an attractive PK, hepatic and hemostatic profile, could provide a highly convenient addition to COVID-19 management, for both female and male patients
- Phase 2 clinical trial results of E4 are awaited with great interest

Key points

- Age, male sex and chronic comorbidities are key predictors of mortality in COVID-19, though some older, comorbid patients have rare unexplained resistance to infection, and some young people without comorbidities experience rare idiopathic severe disease [19]
- COVID-19 goes through different stages, with recommended treatments for each [20]



  - Guidelines for management of SARS-CoV-2 infection in Poland [21]
  - COVID-19 Stage 1: asymptomatic or mildly symptomatic, SpO2 ≥94%
    - Home-based therapy
    - Antipyretics, rest, oral hydration, control of oxygen saturation, inhaled budesonide
    - Antitussives if severe cough, low molecular weight heparin if chronically bed-ridden
  - COVID-19 Stage 2: fully symptomatic, SpO2 <94%
    - Hospitalization, non-ICU
    - Remdesivir IV
    - Oxygen therapy, oral or IV hydration, symptomatic therapy
    - Low molecular weight heparin, dexamethasone if receiving remdesivir and oxygen
    - Antibiotics if secondary bacterial infection
  - COVID-19 Stage 3: respiratory failure (cytokine storm), SpO2 <90%
    - Hospitalization
    - Tocilizumab and/or dexamethasone
    - Oxygen low/high flow, IV hydration, symptomatic therapy
    - Low molecular weight heparin
    - Antibiotics if secondary bacterial infection
  - COVID-19 Stage 4: acute respiratory distress syndrome
    - ICU usually
    - If unsuccessful pharmacotherapy to date
    - Need for mechanical ventilation
    - Dexamethasone +/- (if mechanically ventilated) tocilizumab
    - Oxygen high flow; non-invasive or mechanical ventilation; extracorporeal oxygenation in selected cases
    - Low molecular weight heparin
    - Antibiotics only if secondary bacterial infection
  - US NIH COVID-19 Treatment Guidelines [22] broadly similar, except additional recommendation for anti-SARS-CoV-2 monoclonal antibodies (bamlanivimab plus etesevimab, or casirivimab plus imdevimab) for early stage patients at high risk of disease progression.

- While many therapies are in development, there are unmet medical needs for :
  - ❖ Effective drugs that can be used in both home- and hospital-based settings
  - ❖ Drugs that can be safely combined with other therapies
  - ❖ Drugs that can prevent disease progression
  - ❖ Broad-spectrum therapies that work irrespective of COVID-19 variants

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Moderated Discussion

Prof. Jean-Louis Vincent, Brussels, Belgium

Prof. Vincent thanked the 4 presenters for their very good and informative presentations, then chaired a very lively discussion, with questions to presenters.

Summary of questions and answers

1. **Due to the good rationale for estrogen administration in COVID-19 and other viral infections, could there be some arguments for giving it also in bacterial infections?**
   - ➢ Prof Mauvais-Jarvis: Not known, but it is known for H1N1 and now more COVID-19.
2. **What about other the viral diseases?**
   - ➢ Prof Mauvais-Jarvis: The powerful effect of estrogens on immune cells is a fact, and that alone is enough to pursue investigation. It could be tested in severe H1N1; in other viral diseases, I don't know.
3. **What is your opinion on the route of administration of estrogen?**
   - ➢ Dr. Newson: for estradiol, I would recommend transdermal (patch or gel) due to the VTE risk and poor bioavailability of oral estradiol. It should be absorbed transdermally even in ICU. There is also no reason why men can't have it as well, as it's such a low-risk treatment.
   - ➢ Prof. Mauvais-Jarvis: For people hospitalized with severe COVID-19, transdermal is not going to be an issue. Severe patients with poor hemodynamic condition might have decreased oral absorption. In our trial we decided to give estradiol as an IM depot so as to provide high serum levels with one injection.
   - ➢ Prof. Foidart: I agree that the oral route should be avoided for most estrogens, because only 1-5% of orally administered estradiol gets to the systemic circulation, and so IM or transdermal routes are preferred. It is not the same with E4, which has a very high oral bioavailability. In case E4 would need to be given by a non-oral route, this could be possible, as we already developed a parenteral form for treating newborn babies (FDA and EMA orphan drug designation for treatment of neonatal hypoxic ischemic encephalopathy).
4. **In the very interesting observational studies presented, could the reason that premenopausal females had better outcomes than older women be their age, which is known to be an important prognostic factor?**
   - ➢ Dr. Newson: It is difficult to say for sure, but especially the Oxford study did try to compare like-for-like. I agree that there are limitations in all observational studies, and so we do need prospective randomized controlled studies.

5. **We have not been able to develop many effective medications for COVID-19. If estetrol is shown to be effective, when in the course of the disease should we start it?**
    - Prof. Simon: As early as possible.
    - Prof. Foidart: Agree, if you want to manipulate the immune system, you need to start early.
    - Dr. Newson: Agree, start early, in men as well as women.
    - Prof. Mauvais-Jarvis: Agree, start early, you want to prime the immune system so that it does not get highjacked by the virus.
6. **What if I, as a man, take an estrogen for a limited period of time?**
    - Dr. Newson: You're only going to give estrogens for a short period of time, every effect is reversible anyway, and COVID-19 is a life-threatening disease.

Summary, conclusions, next steps

Dr. Graham Dixon, PhD, Liège

Key conclusions

- Estrogens may represent a highly accessible, affordable, therapeutic option to address respiratory viral diseases, in particular COVID-19.
- Estrogens, and especially E4, offer promising therapeutic potential that has been unexplored to date.
- Results of the first prospective randomized clinical trial of an estrogen in COVID-19 (Mithra's estetrol/E4) are eagerly awaited.

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