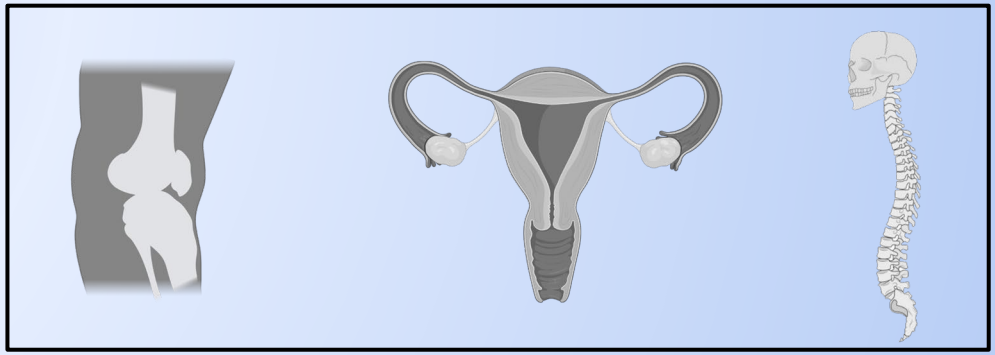

Less Studied Aspects of Long COVID: Reproductive Health Conditions, Connective Tissue Disorders, and Spinal Pathologies in Long COVID and Associated Illnesses

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The National Academies of Sciences, Engineering, and Medicine
Symposium on Long COVID: Examining the Working Definition, June 23, 2023

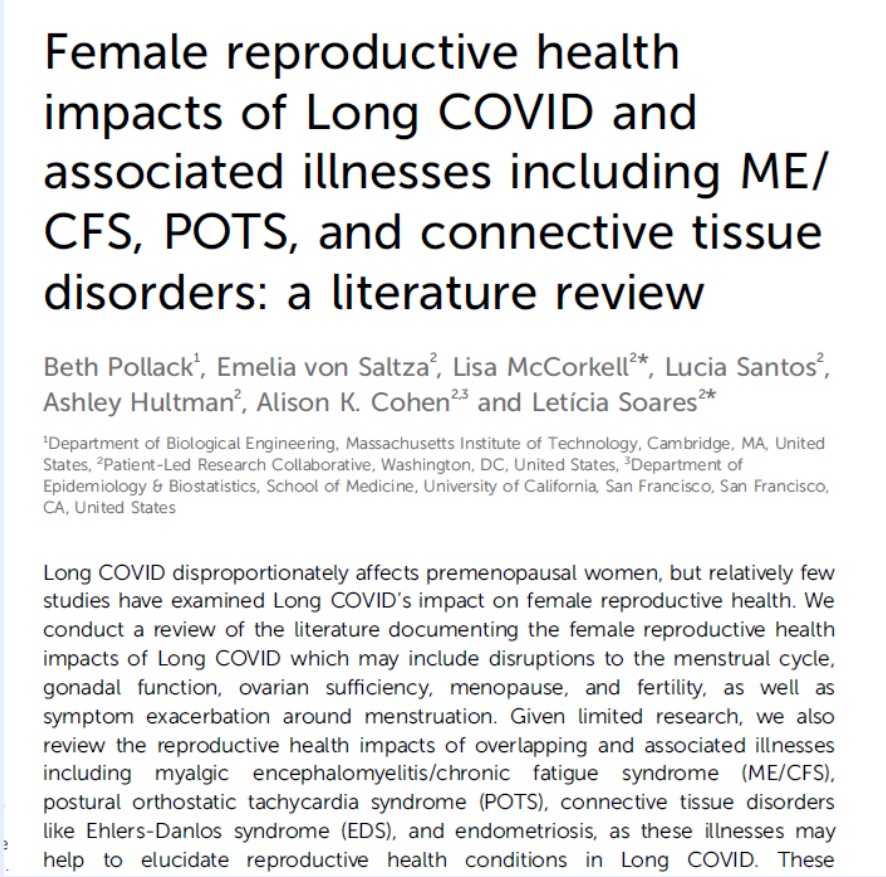
First Review of Reproductive Impacts of Long COVID

Reproductive impacts of Long COVID may include disruptions to:

- Menstrual cycle
- Gonadal function and ovarian sufficiency
- Menopause
- Fertility
- Symptom exacerbation around menstruation

Sex differences:

- Long COVID impacts 2x female patients as male, and may disproportionately impact trans patients as well.
- Pre-menopausal women have a higher risk for Long COVID
- Suggests that sex hormones and sex differences in immune responses to infection may play a role in Long COVID development.



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

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Long COVID disproportionately affects premenopausal women, but relatively few studies have examined Long COVID's impact on female reproductive health. We conduct a review of the literature documenting the female reproductive health impacts of Long COVID which may include disruptions to the menstrual cycle, gonadal function, ovarian sufficiency, menopause, and fertility, as well as symptom exacerbation around menstruation. Given limited research, we also review the reproductive health impacts of overlapping and associated illnesses including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), connective tissue disorders like Ehlers-Danlos syndrome (EDS), and endometriosis, as these illnesses may help to elucidate reproductive health conditions in Long COVID. These

All references found in: Pollack B, von Saltza E, McCorkell L, Santos L, Hultman A, Cohen AK and Soares L (2023) Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review. *Front. Rehabil. Sci.* 4:1122673. doi: 10.3389/fresc.2023.1122673

Female Reproductive Symptoms and Long COVID

Common menstrual cycle irregularities: worsening of premenstrual symptoms and changes to the length of the cycle and duration and intensity of menses.

- 33% to 62% of pre-menopausal Long COVID patients report an exacerbation of their Long COVID symptoms in the days before mendes. (n=1,792 and n=460)
- 34% of menstruating Long COVID patients (n=1,800) reported menstrual issues, which included subsets experiencing abnormally irregular cycles (26%) and heavy periods (19.7%)

Ovarian health: Case reports suggest COVID-19 infection may be associated with long-term decline of ovarian health, including premature ovarian insufficiency.

Premature menopause: May be more prevalent among Long COVID patients in their 40s than in the general population (3% vs 1%).

Critical to further study COVID in pregnant people: A small control matched prospective cohort study in Brazil followed pregnant women after testing positive for COVID-19 (N=84) and 76% developed Long COVID.

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Female Reproductive Conditions in Long COVID, ME/CFS, POTS, and EDS*

Menstrual

- Menstrual cycle irregularities [LC, ME/CFS]
- Excessive menstrual bleeding [LC, ME/CFS, EDS]
- Symptom exacerbation around periods [LC, ME/CFS, POTS]
- Amenorrhea and Oligomenorrhea [LC, ME/CFS, POTS]
- Premenstrual syndrome symptoms [LC]
- Dysmenorrhea [EDS]
- Bleeding between periods [ME/CFS, EDS]

Gynepathologies

- Premature ovarian insufficiency [LC]
- Endometriosis [LC, ME/CFS, POTS]
- Ovarian dysfunction [LC]
- Dyspareunia [EDS]
- Vulvodynia [EDS]
- Ovarian cysts and polycystic ovarian syndrome [ME/CFS, POTS]
- Uterine fibroids and bleeding [POTS]
- Pelvic congestion syndrome [POTS]
- Non-menstrual pelvic pain [ME/CFS]

Fertility and Pregnancy

- Fertility issues [LC, EDS]
- Higher risk of maternal mortality from childbirth [EDS]
- Higher risk of premature birth, miscarriage, stillbirths, placenta previa, preterm premature rupture of membranes, cervical incompetence, antepartum hemorrhage, intra-uterine growth restriction, delivery by C-section, spontaneous abortions, and longer postpartum hospital stays [EDS]
- Pregnancy can trigger and/or alter the course of illness [ME/CFS, POTS]

Menopause

- Premature menopause [LC, ME/CFS]
- Postmenopausal bleeding [LC]
- Symptom exacerbation in perimenopause and postmenopause [ME/CFS]

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Endometriosis

Approximately **10%** of women and people with uteruses develop endometriosis.
Average time to diagnosis: **7-10 years**

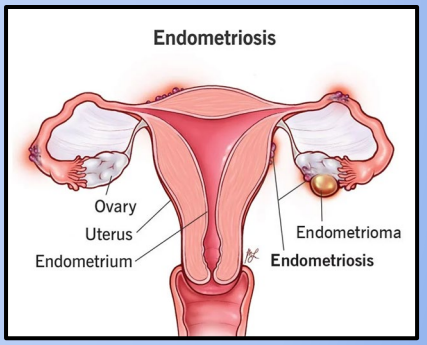

Image source: Cleveland Clinic, 2021

ME/CFS

About 36% of women with ME/CFS (n = 36) report endometriosis.

POTS

20% of women with POTS (n = 65) report endometriosis.

Long COVID

Endometriosis patients may have an increased risk of developing Long COVID (based on a population-based retrospective cohort-matched study using data from electronic health records of non-hospitalized Long COVID patients.) More research is needed to understand contributing factors.

Overlapping Immune and Endocrine Dysfunction

Reduced natural killer cell cytotoxic function, macrophage alterations, lowered cortisol, elevated oxidative stress, and allergies may be implicated in both endometriosis and ME/CFS. Some of these mechanisms may also play a role in Long COVID.

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Endometriosis and Infection Research

Tal Research Group at MIT

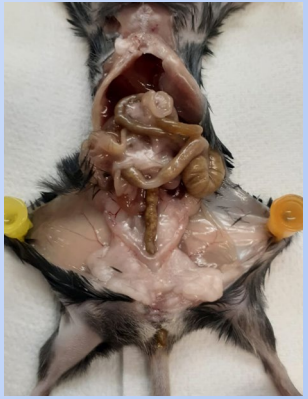
Could infection, such as pathogenic bacteria, contribute to the development of endometriosis?

Muraoka et al found fusobacterium in endometrial tissue of 64% (N=79) of women with endometriosis and 7% of healthy controls (N=76).

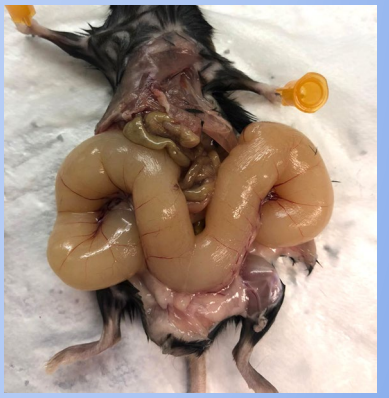
In mouse models of endometriosis, mice inoculated with fusobacteria had increased and larger endometrial lesions.

Antibiotic treatment (metronidazole and chloramphenicol) reduced fusobacterium and the number and size of endometrial lesions in mice.

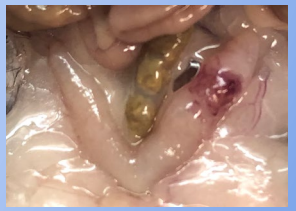
Preliminary Findings: Infection-induced Reproductive Tract Pathologies in Mouse Models



Uninfected:
Normal Uterus and Ovaries



18-Month Infected
Uterus and Ovaries



Source: Tal Research Group at MIT, Grace Blacker, Sarah Galloway, Paige Hansen, Michal Tal

Ayako Muraoka et al. ,Fusobacterium infection facilitates the development of endometriosis through the phenotypic transition of endometrial fibroblasts.*Sci. Transl. Med.*15, eadd1531(2023). doi:10.1126/scitranslmed.add1531

Research Priorities for Female Reproductive Health in Long COVID, ME/CFS, POTS, and EDS

- **How menstruation, pregnancy, sexual function, and menopause impact and are impacted by LC* and comorbidities**
  - Flaring at different times of the menstrual cycle
  - Menstrual cycle impacts on CTD* laxity and CTD related symptoms
  - Fluctuations of MCA* throughout the menstrual cycle
  - Reproductive microbiomes and their impact on RH*
  - Whether sex hormones in the menstrual cycle may increase microclotting and hypercoagulation
- **Sex differences and the role of sex hormones in disease mechanisms and trajectories**
- **Health inequities and underrepresentation in RH research**
- **Rates and mechanisms of RH conditions in LC and associated illnesses including ME/CFS, POTS, CTDs, and IACI***

*LC = Long COVID
*CTD = Connective Tissue Disorder
*MCA = Mast Cell Activation
*RH = Reproductive Health
*IACI = Infection Associated Chronic Illnesses

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Connective Tissue Disorders in Infection-Associated and Complex Chronic Illnesses

Long COVID can cause tissue and organ damage, and more research is needed on its impact on connective tissue.

- 23.35% of Long COVID patients in an EHR study fit within a phenotype characterized in part by having a higher prevalence CTDs.
- Case studies document Long COVID patients developing joint hypermobility post COVID-19.
- ICD-10 Code introduced in 2021 for Other specified systemic involvement of connective tissue (M35.89)

Connective Tissue Disorders like hypermobile Ehlers-Danlos Syndrome (hEDS) and Hypermobility Spectrum Disorders (HSD) are commonly comorbid with ME/CFS and POTS:

ME/CFS

- About half of Long COVID patients meet diagnostic criteria for ME/CFS.
- 12%-19% of ME/CFS patients have hEDS.
- 50%-81% of people with ME/CFS are hypermobile

POTS

- A subset (20%, stats vary) of Long COVID patients have POTS/dysautonomia.
- 18%-31% of POTS patients have hEDS.
- 41%-90% of hEDS and EDS patients respectively have POTS.

Comorbidity is significantly higher than general population prevalence

- EDS: 0.02%-0.2% of the population may have EDS or EDS/JHS (pre-pandemic), 3.4% may have symptomatic hypermobility (joint hypermobility with widespread pain), 12–28% have hypermobility.
- POTS: 0.2-1% of the population may have POTS (pre-pandemic).

Spinal Conditions in Infection-Associated and Complex Chronic Illnesses

Connective tissue laxity can contribute to disabling spinal conditions. More research is needed on spinal conditions in Long COVID, ME/CFS, and associated illnesses like EDS and their roles in pathophysiology.

Spinal Conditions include:

- Upper Cranial instability (including Craniocervical instability and Atlantoaxial instability)
- Chiari Malformation
- Tethered Cord Syndrome
- Can result in neuropathy, compression of brainstem/vascular/nerve compression, cord stretch injury, and cerebral hypoperfusion.
- Symptoms overlap with Long COVID and ME/CFS including neurological, orthostatic and cognitive symptoms, fatigue, and pain.

Statistics

- MRI study: 80% (n=205) of ME/CFS patients have disc bulging or hernias in the cervical spine; 83% have signs of intracranial hypertension; 64% have obstructions in C1–T2; 53% have spinal cord compressions at C5–C6, and 28% at C6–C7.
- 26.5% (n=913) of ME/CFS patients have severe spine problems in an EHR study of ME/CFS clinics.
- 21% of EDS patients have craniocervical instability and 40% of EDS patients have tethered cord syndrome in an EHR study of EDS clinics.
- Studies have found similar spinal conditions in fibromyalgia patients.

Possible Roles of Infection, Inflammation, and Mast Cell Activation?

- Mast cell mediators like histamine and tryptase can damage collagen.
- Klinge et al found inflammatory cell invasion (including mast cells) in the filum terminale of hEDS tethered cord surgical patients, and their fillum was half as elastic as non-hEDS tethered cord surgical patients, increasing risk for cord stretch injury.
- HHV-6 viral miRNA was found in the brain and spinal cords of ME/CFS patients, including cervical, lumbar, and sacral nerve roots. (Kasimir, et al)

Research and Clinical Implications

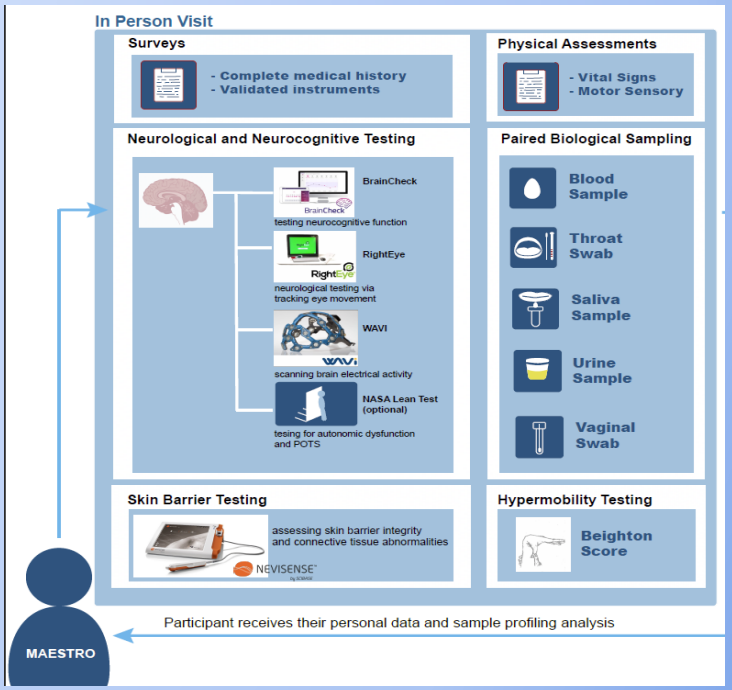
Include Reproductive Health, Connective Tissue Disorders, and related Spinal Conditions in research and clinical approaches to studying, diagnosing, and treating Long COVID and associated illnesses.

♦ **Clinical studies and trials:** Consider screening for these conditions as a component of studies to help advance understanding of phenotypes, disease mechanisms, and their roles in the overall clinical picture and disease trajectories of Long COVID and infection-associated illness

♦ **Reduce diagnostic delays:** Clinicians should consider screening for these lesser studied aspects of Long COVID in patients with relevant symptoms, as well as screening for co-occurring and associated illnesses like ME/CFS, MCAS, and POTS.

MIT MAESTRO - Tal Research Group
Largest clinical study in MIT history

Neurological testing and deep immune profiling of Long COVID, acute Lyme disease, and Chronic Lyme disease. Aims to expand to ME/CFS and other infection-associated diseases.



Assesses or screens for reproductive health, hypermobility, spinal conditions, and other co-occurring conditions as a part of the study

Acknowledgements

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My Co-Authors of the Review on Female Reproductive Health Impacts of Long COVID and Associated Illnesses: Emelia von Saltza, Lisa McCorkell, Lucia Santos, Ashley Hultman, Alison K. Cohen, and Letícia Soares

Tal Research Group at MIT

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