

Female hormones and COVID-19

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Summary Points

- Estrogen is known to improve the way cells that fight infections work and can increase the number of these cells
- The risk of death from COVID-19 for women >50 years taking HRT has been shown to reduce by more than 50%⁴
- Low estrogen and low testosterone in women are likely to be associated with Long Covid
- Anecdotally many women with Long Covid have improved with estrogen and testosterone replacement
- The majority of women have more benefits than risks from taking HRT

Relevance of estrogen to COVID-19 infections

There are marked differences in morbidity and mortality from COVID-19 between the sexes, with men at a higher risk of severe COVID-19 disease and death than women.

An early study from Wuhan has shown that women with low estrogen levels had more severe infection with COVID-19².

An analysis of electronic health records of nearly 70,000 patients who tested positive for COVID-19 from 17 countries has shown that women taking HRT were **more than 50% less likely to die from COVID-19 compared to women not taking HRT**⁴.

Estrogen and immunity (Figures 1 and 2)

It is well established that there are differences between female and male sexes in responses to infections, with females having better immune response (ability to fight infections) than males. There is evidence that estrogen can work as an anti-viral for other infections including hepatitis C, Ebola and HIV infections.

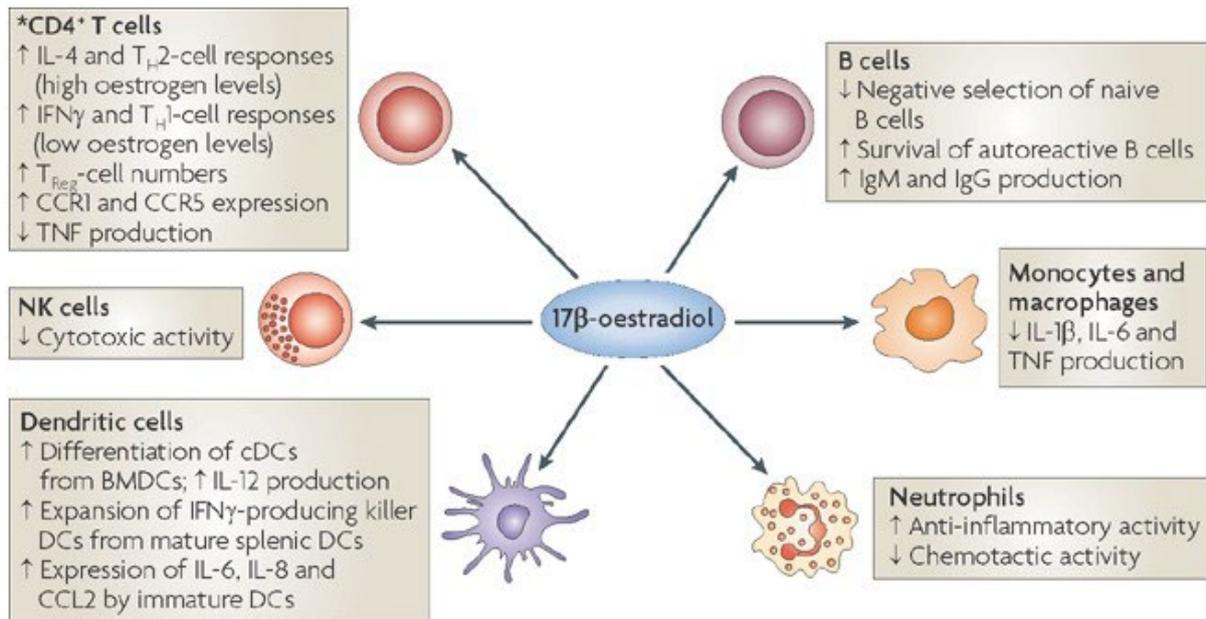
There are numerous ways that estrogen can influence the response to COVID-19 infection especially with the way it improves women's immune function as well as working in a protective way on the blood vessels and cardiovascular system.

There are estrogen receptors on all cells that fight infections. Estrogen works to improve the number, genetic programming and lifespan of all immune cells including neutrophils, macrophages, dendritic cells and natural killer cells⁵.

Estrogen also regulates the production of numerous cytokines (chemicals that are produced by these immune cells) including interleukin-6, interferon and tumour necrosis factor. Estrogen can block the production of interleukin-6 which is important in the cytokine storm which occurs in some people with severe COVID-19 infections. A cytokine storm is when large quantities of cytokines are produced in the body which have a detrimental effect. This is because these cytokines then lead to organ and tissue damage (especially in the lungs)⁶.

More specifically to COVID-19 infections, estrogen can inhibit angiotensin-converting enzyme (ACE) which then has a protective effects on the heart, lung, kidneys, central nervous system and gut⁷.

Figure 1 Estrogen and its effect on immune cells



Hormones, menopause and HRT

The menopause is a long-term hormone deficiency leading to health risks if not appropriately managed with hormone replacement therapy (HRT). These include increased risk of cardiovascular disease, type 2 diabetes, obesity, osteoporosis, depressive symptoms and dementia.

We now have clear, evidence-based guidelines including from NICE available to ensure women have individualised care and treatment for their perimenopause and menopause^{8,9}. These guidelines clearly state that the benefits of HRT outweigh the risks in the majority of women. There is a lower risk of death from all causes for women who take HRT in the long term - more than 18 years^{10,11}. Research, including Cochrane data, has shown that women taking HRT have a lower risk of heart disease, type 2 diabetes and obesity^{12,13}.

Despite overwhelming evidence to support the safety and effectiveness of HRT, only the minority of menopausal women take HRT and women from low socio-economic backgrounds are 29% less likely to be given HRT – despite these women often having a higher risk of heart disease so are more likely to benefit from taking HRT¹⁴.

However, many women and healthcare professionals are still worried about the perceived risks of HRT. Much of the negativity regarding HRT stems from the misinterpretation of the Women's Health Initiative (WHI) study in 2002, which led to a worldwide reduction in HRT use¹⁵. The subsequent sub-

analysis of this study revealed reassuring and positive results to support the use of HRT including evidence that women taking estrogen only HRT have a lower future risk of breast cancer and also a lower risk of dying from breast cancer.¹⁶

There is now robust evidence which shows that transdermal estrogen (given as a patch, gel or spray) in association with natural micronised progesterone represents the optimal HRT regimen¹⁷. Transdermal estrogen is the preferred route of administration because, in contrast with oral estrogen, it is not associated with an increased risk of clot.

Long Covid and hormones

Long Covid (sometimes called Post-Covid-19 syndrome) occurs in some people who have had an infection with Long Covid in the past and have symptoms which last for more than 12 weeks and are not explained by an alternative diagnosis.

In women who develop COVID-19, being post-menopausal has been independently associated with more severe infection^{18,19}.

The largest group of patients with Long Covid appears to be women in their early 50s. The average age of the menopause is 51 and the majority of women are perimenopausal in their 40s. Many of the symptoms due to Long Covid are similar to perimenopausal and menopausal symptoms.

Similar to other post-viral syndromes, Long Covid is more common in women, with those coming to the end of their reproductive lives seem to be particularly affected. It is likely that the coronavirus directly affects the way the ovaries work and produce hormones.

The virus responsible for COVID-19 enters cells via a specific receptor, ACE 2, which is present on the ovary. The hormones estrogen and testosterone are both produced by the ovaries and their levels reduce during the perimenopause and menopause.

An online survey of 1,294 women with Long Covid found that 73% of women reported that their periods have changed since having symptoms of COVID-19. Furthermore, 72% of women reported that their symptoms of Long Covid changed in relation to their menstrual cycle with 77% of women reporting their symptoms being worse prior to or during their periods (when hormone levels are at their lowest).

These symptoms are likely to be related to low estrogen and testosterone levels so consideration should be given as a priority to replacing these low hormone levels with the right dose and type of HRT.

All women who attend a Long Covid clinic need to be asked about the possibility of being perimenopausal or menopausal. Before the attend the clinic, they should be encouraged to download the free balance app and create a health report which includes a menopause symptom questionnaire - www.balance-app.com

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