



HEALTH RISKS OF ESTROGEN FOR MALES

From Emerging and accumulating safety signals for the use of estrogen among transgender women, Schwartz, L., Lal, M., Cohn, J. et al.

The use of exogenous estrogen (typically with anti-androgens) in males to induce female secondary sex characteristics is associated with a range of significant health risks across multiple organ systems. This document summarizes key adverse outcomes and safety signals—new observed effects that suggest association with estrogen use—identified in the medical literature.

Previously identified adverse physiological effects

- **Cardiovascular risks:** Risk of both venous thromboembolism (VTE) and stroke are significantly elevated. Emerging evidence suggests that cardiovascular risks escalate significantly with prolonged estrogen use. VTE incidence became 5.1 times higher after 2 years, and ischemic stroke incidence rose to nearly 10 times higher after 6 years.
- **Fertility risks:** Range in ability to produce sperm. Several studies report that some fraction of patients can produce sperm, while others have complete inability to produce sperm, along with testicular atrophy and abnormal changes to testicular tissue. Estrogen and anti-androgen treatment also causes higher proportions of sperm abnormalities (i.e., low total sperm count, low sperm concentration, poor sperm motility), however, some of these effects may be reversible once estrogen use has stopped.
- **Cognitive impairment:** A systematic review of cognitive impairment among young adults [62] found no effect of hormones. However, a study with a larger sample size and long-term follow-up (average 25.8 years) found lower scores in information-processing speed and episodic memory than men not using estrogen and women (matched in education and age). There is a known doubling of relative risk for probable dementia after an average follow-up of 4 years for older adults.

Emerging safety signals: other associated adverse physiological effects

- **Overall health risks and early mortality:** Studies show that males who use estrogen die younger than expected compared to other men and women. The overall survival odds decreased within a few years of starting estrogen, and continued to decrease over time. The major causes of death included cardiovascular disease, cancer, infection-related disease, and suicide. (Note that a recent Finnish record study found that suicide rates of young people were correlated with mental health issues (as measured by specialist psychiatrist visits) rather than gender dysphoria diagnosis or associated medical interventions.)
- **Autoimmune disease:** Studies are inconclusive, but suggest a possible increased autoimmune disease risk for males using estrogen. Several case studies show rheumatoid arthritis (1), ankylosing spondylitis (1), systemic lupus erythematosus (SLE, 4), skin lupus erythematosus (1), systemic sclerosis (4), and dangerous autoimmune disease progression.
- **Diabetes:** Estradiol, with or without anti-androgen, decreases lean mass, increases fat mass, and may worsen insulin resistance.
- **Pancreatitis:** Males who use estrogen could be at a higher risk for severe pancreatitis and gallstone pancreatitis.



- **Thyroid cancer:** Experimental studies indicate a possible role of estrogen in the development of thyroid cancer, specifically a more aggressive type.
- **Testicular cancer:** Case studies suggest a significantly higher risk of testicular cancer with estrogen use.
- **Breast cancer:** A recent systematic review and meta-analysis of the incidence of breast cancer among males who use estrogen indicate a significant increase in breast cancer risk.
- **Adverse drug reaction reports:** Adverse drug reactions (ADRs) in the US FDA Adverse Event Reporting System (FAERS) database for males who use estrogen included tumors (benign, malignant, and unspecified, including cysts and polyps). In the comparable French database, the main ADR was meningiomas, a tumor that grows from the membranes that surround the brain and spinal cord, followed by cardiovascular events.

Physiological effects of estrogen on the male brain

- **Cognitive Decline:** Animal studies suggest estrogen use is associated with an increase in ventricular volume and a decrease in brain volume, possibly by lowering water content in brain cells, causing cognitive decline comparable to age-related decline.
- **Major Depressive Disorder:** Use of estrogen and antiandrogens may increase risk of developing major depressive disorder by reducing serum BDNF (Brain-Derived Neurotrophic Factor), thought to be associated with psychosocial “stress.” In addition, major depression is associated with reduced hippocampal (and frontal lobe and gray and white matter) volume. Higher levels of estradiol (a type of estrogen) in the blood were associated with increased symptoms of depression in men under 60 and elevated depression and anxiety scores in boys.

The poorly understood but significant rise in gender dysphoria diagnoses among young people in recent decades necessitates prioritizing adequate long-term follow-up studies. Given the increasing reports of harm and regret, and the lack of research demonstrating the safety and efficacy of current treatment options for this vulnerable population, it is imperative that future research endeavors prioritize the identification of safe and effective interventions. Furthermore, it is essential to enhance our understanding of and ability to communicate potential risks, including life-altering and permanent adverse effects, to patients and families. This will enable informed decision-making and minimize harm.

To view the publication and citations, scan the QR code or go to
<https://link.springer.com/article/10.1007/s44192-025-00216-3>.

