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The American College of Pediatricians urges FDA to undertake a comprehensive safety review of the use of estrogen in males and to issue a Black Box Warning.

My name is Dr. Michelle Anne Cretella, chair of the sexuality committee of the American College of Pediatricians. The American College of Pediatricians is the leading U.S. medical organization protecting gender dysphoric children and adolescents from the medical harms of sex-rejecting social, chemical, and surgical interventions. We are an organization of physicians and allied health professionals from across the United States and 5 additional countries dedicated to the practice of evidence-based pediatric medicine and the medical ethics principle of first do no harm. Our mission is to promote ethically and scientifically sound policy to ensure the optimal physical and emotional health of children and young adults. The American College of Pediatricians therefore urges the FDA to conduct a comprehensive investigation into the alleged safety and benefits of estrogen use in males seeking feminization, and to issue a Black Box warning based on estrogen's well established elevated cardiovascular risk profile in this population.

Several systematic reviews since 2019 have found low or very low certainty evidence for alleged positive outcomes of hormone use in both female and male minors [1,2,3,4,5,6,78,9]. Since minors might continue to identify as the opposite sex across their lifespan, research concerning potential risks and benefits of hormone use among adults is also pertinent to them. Bränström and Pachankis found no benefit to hormones for male or female adults across any of their outcome measures [10]. What is more troubling, a Cochrane review of studies meant to assess the impact of estrogen on adult males identifying as female found no qualifying completed studies [11]. While the scientific literature fails to provide evidence of estrogen's alleged benefits to males seeking feminization, it does demonstrate concerning safety signals across several organ systems. These include the well-defined elevated risks for venous thrombo-embolism and infertility, as well as potential increased risk for cognitive impairment,

long-term psychological decline, adverse metabolic alterations, autoimmune disorders and certain cancers [12]. Clearly, the FDA has ample evidence to conduct a comprehensive safety review of the off-label use of estrogen among males of all ages.

There is already significant evidence of estrogen causing serious harm to males when used to feminize their physical appearance. Research consistently indicates that males using estrogen experience increased cardiovascular risks compared to their male peers not taking estrogen [13,14,15,16]. For example, a meta-analysis involving over 15,000 males on estrogen found their rate of venous thrombo-embolism was 2.2 times higher than that of their male peers not taking estrogen [14]. Another comprehensive review concluded there was “strong evidence” that estrogen use in trans-identified males increases their risk for venous thrombo-embolism over fivefold [15]. For this reason, the American College of Pediatricians urges the FDA to fulfill its mission under 21 C.F.R. § 201.80(e) to mandate the appropriate Boxed Warning.

References

1. Cass H. Independent review of gender identity services for children and young people; 2024. https://webarchive.nationalarchives.gov.uk/ukgwa/20250310143933/https://cass.independent-review.uk/home/publications/final-report/.

2. Brignardello-Petersen R, Wiercioch W. Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. 2022. https://ahca.myflorida.com/letkidsbekids/docs/AHCA_GAPMS_June_2022_Attachment_C.pdf

3. Ludvigsson JF, Adolfsson J, Höistad M, Rydelius PA, Kriström B, Landén M. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. Acta Paediatr. 2023;112:2279–91.

4. National Institute for Health and Care Excellence. Evidence review: gender-affirming hormones for children and adolescents with gender dysphoria. NICE; 2020. https://webarchive.nationalarchives.gov.uk/ukgwa/20250310144323mp_/https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_Gender-affirming-hormones_For-upload_Final.pdf

5. Zepf FD, König L, Kaiser A, Ligges C, Ligges M, Roessner V, et al. Beyond NICE: AktualisiertesystematischeÜbersichtzurEvidenzlageder Pubertätsblockade und HormongabebeiMinderjährigenmitGeschlechtsdysphorie. Z Kinder JugendpsychiatrPsychother. 2024. https://doi.org/10.1024/1422-4917/a000972.

6. McDeavitt K. Paediatric gender medicine: longitudinal studies have not consistently shown improvement in depression or suicidality. Acta Paediatr. 2024;113:1757–71.

7. Taylor J, Mitchell A, Hall R, Langton T, Fraser L, Hewitt CE. Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic review. Arch Dis Childhood. 2024;109:s48–56.

8. Miroshnychenko A, Ibrahim S, Roldan Y, Kulatunga-Moruzi C, Montante S, Couban R, et al. Gender affirming hormone therapy for individuals with gender dysphoria aged <26 years: a systematic review and meta-analysis. Arch Dis Child. 2025;110:437–45.

9. Treatment for Pediatric Gender Dysphoria. US Department of Health and Human Services; 2025. Available from: https://opa.hhs.gov/sites/default/files/2025-05/gender-dysphoria-report.pdf

10. Bränström R, Pachankis JE. Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study. AJP. 2020;177(8):727–34. (see also: Bränström R, Pachankis JE. Correction to Bränström and Pachankis. AJP. 2020;177(8):734–734.)

11. Haupt C, Henke M, Kutschmar A, Hauser B, Baldinger S, Saenz SR, et al. Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women. Cochrane Database Syst Rev. 2020. https://doi.org/10.1002/14651858.CD013138.pub2.

12. Schwartz L, Lal M, Cohn J, Mendoza CD, MacMillan L. Emerging and accumulating safety signals for the use of estrogen among transgender women. Discov Ment Health. 2025 Jun 12;5(1):88. doi: 10.1007/s44192-025-00216-3. PMID: 40506545; PMCID: PMC12162459.

13. Glintborg D, Christensen LL, Andersen MS. Transgender healthcare: metabolic outcomes and cardiovascular risk. Diabetologia. 2024;67(11):2393–403.

14. Van Zijverden LM, Wiepjes CM, Van Diemen JJK, Thijs A, Den Heijer M. Cardiovascular disease in transgender people: a systematic review and meta-analysis. Eur J Endocrinol. 2024;190(2):S13-24.

15. Irwig MS. Cardiovascular health in transgender people. Rev EndocrMetabDisord. 2018;19(3):243–51.

16. Franco-Moreno A, Ryan P, Muñoz-Rivas N, Valencia J, Torres-Macho J, Bacete-Cebrián S. Riesgo de tromboemboliavenosaen población transgéneroenterapia hormonal: unarevisiónsistemática y metaanálisis. Med Clin. 2025;164(12): 106921.