# Catechol-O-Methyl Transferase Inhibitors and 2-Methoxyestradiol Suppress Leiomyoma Cell Proliferation: Potential Medical Therapy for Uterine Fibroids

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**Objectives:** Due to minimal success with nonsurgical treatment options for uterine leiomyomas, it is imperative that other compounds be tested for potential preventive/therapeutic use. Since estrogen plays a pivotal role in the development and progress of leiomyomas, it is rational to hypothesize that targeting estrogen metabolism or using certain estrogen metabolites possessing antiestrogenic effects might be a useful treatment of leiomyomas.

**Methods:** In the current study, we tested the effect of estradiol (E2) and its metabolite 2-hydroxyestradiol (2-OHE2), with or without catechol-O-methyl transferase inhibitor 10 (COMT-I), on ELT-3 rat leiomyoma cell proliferation and the expression of adenovirus-estrogen response element luciferase (AdERE-Luc) reporter vector. In addition, we tested the effect of 2-methoxyestradiol (2-MeOHE2) on the growth of leiomyoma cells in culture.

**Results:** Our data indicated that COMT-I reversed the proliferative effect of E2 on ELT-3 and reduced the E2-induced upregulation of AdERE-Luc reporter. Furthermore, 2-OHE2 antagonized the effect of E2 on cell proliferation and AdERE-Luc activation. 2-MeOHE2 exhibits a biphasic effect on leiomyoma cells. With relatively low concentration levels ($10^{-10}$–$10^{-8}$ M), it is mitogenic, while at pharmacological concentrations ($10^{-7}$–$10^{-6}$ M), it is antiproliferative. Our data also demonstrated that the antimitogenic effect of 2-MeOHE2 is associated with downregulation of the vascular endothelial growth factor (VEGF), Cyclin D, and bcl2, and up-regulation of Bax.

**Conclusion:** The results of the current study suggest the potential usefulness of COMT-I as well as the estrogen metabolite 2-MeOHE2 as agents for nonsurgical management of uterine leiomyomas.