Case reports regarding endometrial hyperplasia and carcinoma, their co-existence and the possible relationship of endometrial hyperplasia and ovarian abnormalities appeared by the late 19th century. Evidence continued to develop in the early 20th century related to the relationship between estrogen and endometrial cancer as well as between endometrial hyperplasia and carcinoma. In 1975 there appeared the first two observational studies reporting the relationship between unopposed estrogen use in the menopause and endometrial cancer in women with a uterus. Although data prior to 1975 had supported progestin's ability to prevent estrogenic stimulation of the endometrium it was not until the late 1980's that large clinical trials of estrogen and progestogen combinations were successfully initiated. These and other trials helped to define the doses and durations for the components in menopausal hormone therapy. The initial cyclic use of progestins, associated with regular monthly withdrawal bleeding was eventually largely replace by continuous combined therapy, with the hope of achieving amenorrhea. However, continuous combined menopausal hormone therapy was associated with irregular bleeding and spotting in many patients. By the late 1990's work was underway on a new approach to menopausal therapy, one partnering estrogen with a SERM. This approach, the Tissue Selective Estrogen Complex (TSEC) when using conjugated estrogens and bazedoxifene has prevented the estrogenic stimulation of the endometrium, treated menopausal vasomotor symptoms, helped to prevent osteoporosis, and achieved amenorrhea rates similar to placebo while maintain an acceptable safety profile.

7. Pickar JH, Yeh I-T, Bachmann G, Speroff L. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. Fertility and Sterility