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An update on non-uterine gynaecological effects on raloxifene

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Levormeloxifene is a Selective Oestrogen Receptor Modulator (SERM) that was developed by Novo Nordisk to treat and prevent postmenopausal osteoporosis. In 1998, phase III trials of levormeloxifene were suspended after 10 months because of adverse events that were mainly gynacological, but also gastrointestinal and genitourinary. Patients treated with levormeloxifene had a 3.5-fold increase in Relative Risk (R.R.) compared with placebo of developing utero-vaginal prolapse, and 5-fold increase relative R.R. to placebo of developing urinary incontinence. There was also a marked increase, which was statistically significant, in endometrial disorders (mostly endometrial thickness), leukorrhea, and uterine disorders (increased uterine volume on ultrasound).

Postmenopausal atrophy of support elements is a precipitating factor in the development of genital prolapse. It is unclear if this is simply an aging phenomenon or related to oestrogen deprivation. There have been no previous randomised trials analysing this. With aging, connective tissue is weakened due to decreases in collagen content. Traditional teaching espouses oestrogen will improve urinary control in postmenopausal women.

In a sub-study of the HERS (Heart oestrogen/progesterone Replacement Study) [1] 1525 women less than 80 years old with heart disease who had at least one episode of incontinence per week were randomised to placebo versus conjugated equine oestrogen/medroxy progesterone acetate for 4.1 years. The number of incontinence episodes per week increased by an average of 0.7 in the HRT group and decreased by 0.1 in the placebo group ($P<0.001$). Uterine wet weight of oophorectomised rats has often been used as a preclinical marker of oestrogenic activity. Oestrogen, as well as levormeloxifene, results in increased uterine growth in oophorectomised rats [2]. Raloxifene does not increase uterine wet weight or cause uterine hypertrophy in such experimental animals [3].

In order to judge raloxifene's effect on the frequency of surgery for pelvic floor relaxation, the data on safety from three large clinical trials were analysed blindly for surgical events [4]. These included two osteoporosis prevention trials in younger women and one osteoporosis treatment study in older women. All three trials were double-blind, randomised, and placebo-controlled. There were 6926 women with uteri at baseline followed for 3 years. Women with prior hysterectomies were excluded. Surgical procedures performed for pelvic organ prolapse or urinary incontinence included hysterectomy, burch retropubic bladder neck suspension, Marshall–Marchetti and colpocystorrhaphy. 103 women (1.5%) had surgical procedures. 34 hysterectomies for reasons other than pelvic floor relaxation were excluded. These included bleeding, leiomyomas, ovarian cancer, ovarian cyst, cervical cancer and cervical dysplasia. Sixty-nine surgeries were reported for pelvic organ prolapse and/or urinary incontinence. The rate of surgery in the placebo group was 6.3/1000 women years versus 3.2/1000 women years in the raloxifene-treated patients. This yields a RR = 0.50 (95% Confidence Interval (CI), 0.31–0.81). In other words, raloxifene was associated with a 50% reduction in the risk of pelvic floor surgery ($P<0.005$). This was observed within 9 months of treatment and was sustained throughout the 3-year treatment.

Overall, the rate of surgery in all women in the study was 4.2/1000 women years. This is comparable to published results from epidemiological studies. Although these trials were not designed to assess the effect of raloxifene on the pelvic floor and there was no systematic evaluation for pelvic organ relaxation, the large number of women in this analysis and the highly significant reduction in pelvic floor surgery associated with raloxifene, and the fact that there was no therapy difference for the first 9 months all suggest that the current findings are significant.

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In summary, raloxifene treatment for 3 years does not increase pelvic floor relaxation. An apparent protective effect (50% reduction) warrants further investigation.

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