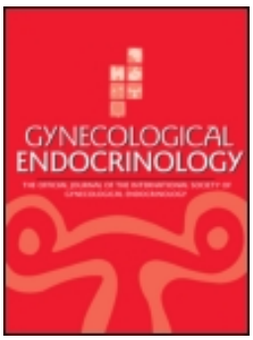

Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: http://www.tandfonline.com/loi/igye20

Femoston®: Effects on bone and quality-of-life

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To cite this article: J-J. Amy (1996) Femoston®: Effects on bone and quality-of-life, Gynecological Endocrinology, 10:sup4, 115-116, DOI: 10.3109/09513599609116215

To link to this article: http://dx.doi.org/10.3109/09513599609116215

Endometrial safety of Femoston®

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Estrogen replacement therapy increases the risk of endometrial hyperplasia and cancer, the reduction of which depends upon supplementation with progestogen. In combined hormone replacement therapy, an estrogen antagonist (progestin) is added sequentially to the estrogen treatment. Histologically, adequate progestogen response results in the disappearance of mitosis in the glandular component of the endometrium, together with a secretory transformation, or atrophic aspect, of the mucosa. Femoston® is a combined sequential treatment using 2 mg/day 17β-estradiol supplemented with 10 mg dydrogesterone (daily for 14 days every 28 days). The safety of Femoston® therapy has been assessed in 2 studies; a dydrogesterone dose–ranging study (5–20 mg dydrogesterone) and a 1-year treatment study using 10 mg dydrogesterone.

In the dose–ranging study, final endometrial histology was available for 286 women who had received at least three cycles, and 271 women who had received at least six cycles, of sequential treatment. Adequate progestational response of the endometrium was found in 94% of women in the 5 mg dydrogesterone group (lower 95% CL: 85.2); 97% in the 10 mg group (lower 95% CL: 91.6); 98% in the 15 mg group (lower 95% CL: 93.6) and 98% in the 20 mg group (lower 95% CL: 90.9). Thus, in all groups, the response rate was ≥ 94%, whilst the lower 95% CL remained above 90% in all but the 5 mg dydrogesterone group. From these data it was considered that sequential 10 mg/day dydrogesterone is the optimum dose to oppose daily 2 mg/day estradiol and confers sound endometrial protection.

In the long-term 2 mg estradiol/10 mg dydrogesterone endometrial safety study, final endometrial histology was evaluable for 146 of the 150 patients who received treatment for 1 year. The success rate for progestational response in this sample was 97%.

These two studies confirm the safety, as determined by endometrial histology, of Femoston® therapy. The combination of both these hormones within a single Femoston® tablet should also allay fears regarding increased risk of endometrial hyperplasia and neoplasia through patient non-compliance with estrogen/progestogen therapy.

Femoston®: effects on bone and quality-of-life

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Depletion in ovarian follicles at the time of the menopause, with the subsequent decline in peripheral estrogen levels, can result in the emergence of a complex syndrome, having both physical and psychological components, including climacteric symptomatology and an increased risk of osteoporotic fracture. Evidence is accumulating which confirms that hormone replacement therapy (HRT) relieves the acute symptoms of estrogen deficiency and reduces some long-term effects of estrogen depletion.

Femoston® is a new oral sequential hormone replacement whereby 2 mg of micronised 17β-estradiol is taken daily, together with 10 mg of dydrogesterone (an orally active pure progestogen), daily for two out of every four weeks. Femoston® has been shown to have beneficial effects on the acute symptoms of the climacteric, on bone, and on quality-of-life. In a long-term study of 186 post-menopausal women who received Femoston® for 1 year, De Jonge *et al.* (1993) showed a clear reduction in the percentage of women bothered by hot flushes, night sweats, attacks of diaphoresis and sleeping disturbances after six weeks, and also throughout the remainder of the study. In addition, the number of women bothered by vaginal dryness and dyspareunia also decreased over the treatment period.

The bone sparing effects of Femoston® have also been demonstrated. Haenggi *et al.* (1993) showed that, compared with untreated controls, Femoston® significantly increased bone mineral density (BMD)

in the lumbar spine at 6 and 12 months ($p \leq 0.01$) and in the upper femur and Ward's triangle at 12 months ($p \leq 0.01$) whilst Lees *et al.* (1995) showed Femoston® to significantly increase BMD measurements in the lumbar spine over 12 and 24 months of treatment. Lees *et al.* (1995) also showed an extra increase in BMD in lumbar spine in patients switched from conjugated equine estrogens (0.625 mg) to estradiol (2 mg) .

In conclusion, Femoston®, a new combination HRT, offers effective control of climacteric symptoms and a reduction in the risk of osteoporotic fracture, thus improving quality-of-life in (post)menopausal women.

Genitourinary disturbances and HRT

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There is evidence proving a direct action of estrogens on the lower urinary tract structures. The common embryologic origin of both the genital and lower urinary tracts accounts for their ability to respond to sexual steroids. This explains the role of ovarian steroids in the regulation of the urinary function in women, and, in consequence, the urinary disturbances following the postmenopausal hypoestrogenic situation.

The majority of studies are unable to prove a clear relationship between the menopause and the onset of urinary stress incontinence, but the link is more evident concerning the so-called 'sensitive urinary syndrome' which includes urgency incontinence, frequency and nocturia. The vaginal atrophy secondary to menopausal hypoestrogenism creates a situation favoring urinary infections. During reproductive age the vaginal flora is maintained by a low pH created through the production of lactic acid by lactobacilli. With atrophy, glycogen production decreases, vaginal pH increases and lactobacilli are replaced by enterobacteriae. This, together with the distal urethral atrophy, favors ascending colonization and recurrent urinary infections.

The goal of hormone replacement therapy is the improvement or disappearance of symptoms, the prevention of the long-term metabolic consequences and reverse the genito-urinary changes. This can be obtained by administering 2 mg of micronized estradiol, 0.625 mg of conjugated equine estrogens or 50 μg patches. In case of local administration, the effects can be achieved through two different ways: local diffusion or vaginal absorption *via* general circulation. It will depend on the product, the excipient and the dose delivered locally.

In general terms, the published evidence does not give support to the effectiveness of estrogen replacement by any route as a therapy for already-established genuine urinary incontinence in postmenopausal women. Conversely both oral or local approaches to estrogen replacement proves effective in reversing sensitive symptoms, thus increasing patient's comfort in urinary and genital function.

There are several uncontrolled and one placebo-controlled study showing that low-dose treatments, both oral or local, are able to reverse vaginal atrophy and prevent the recurrence of infections. The effectiveness of such treatments in preventing recurrence after surgery should also be prospectively evaluated.