A5. SAFETY WITH REGARD TO THE ENDOMETRIUM IN THE ESPRIT TRIAL

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Estrogen in the Prevention of Reinfarction Trial (ESPRIT) was a placebo-controlled randomised control trial (RCT) of 24 months oestradiol valerate (2 mg) to determine if it could prevent reinfarction or cardiac death in women who had had a myocardial infarction. The trial did not show any benefit from oestradiol valerate, but offered the opportunity to observe the effects of unopposed oestradiol on the endometrium.

Subjects had a median age of 62.5 years and had been, on average postmenopausal for 16 years. The hysterectomy rate was 24% and 11% had taken prior hormone replacement therapy (HRT). The mean body mass index was 26 kg/m^2. Non-compliance with oestradiol rose from 29% at 3 months to 57% at 24 months, compared with 23% and 37%, respectively, for placebo. Bleeding was the major reason for non-compliance, with 56% reporting bleeding in the oestradiol arm compared with only 7% for placebo treated patients. Bleeding began within 6 months in 75% of the bleeders. Of the 208 women who bled in the oestradiol group, 189 had an endometrial biopsies with the following results; 112, no pathology; 57, simple hyperplasia; 12, complex hyperplasia; 8, atypical hyperplasia; 0, endometrial carcinoma. All complex and atypical hyperplasia were reversed with medroxyprogesterone acetate, and cessation of oestradiol in the latter cases.

Comment: Oestradiol valerate commonly induced bleeding, but rarely produced atypical hyperplasia. The reason for the occurrence of atypical hyperplasia in 4% is not known.

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A6. FULVESTRANT ('FASLODEX') PREVENTS ENDOMETRIAL GROWTH: A PHASE I TRIAL

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Tamoxifen has been the mainstay of breast cancer treatment for many years. However, tamoxifen has partial oestrogen agonist activity that can increase the risk of endometrial cancer with long-term exposure. Fulvestrant ('Faslodex') is a new oestrogen receptor antagonist with no agonist effects. This double-blind, randomised trial evaluated the effects of fulvestrant on the endometrium of healthy post-menopausal volunteers, when given alone and in combination with ethinyloestradiol (EE). Following a 14-day screening period during which volunteers were assessed for a positive response to EE, 30 volunteers were randomised to receive fulvestrant 250, 125 mg or placebo as a single intramuscular injection (providing pharmacokinetic exposure for at least one month). Two weeks post-injection, volunteers received 2 weeks of concurrent exposure to EE 20 μg /day. Endometrial thickness was measured pre- and post-screening, pre-dose, and on days 14, 28, and 42 post-treatment. Fulvestrant 250 mg significantly inhibited EE-induced endometrial thickening compared with placebo (P=0.0001). Neither fulvestrant 125 or 250 mg demonstrated oestrogenic effects on the endometrium during the 14-day treatment period. Fulvestrant was well tolerated and reduced the incidence of EE-related side-effects. Fulvestrant 250 mg is an oestrogen receptor antagonist with no evidence of agonist activity in the endometrium of healthy post-menopausal women.

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