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P183 THE EFFECTS OF ICI 182,780, A PURE ANTI-OESTROGEN, ON REPRODUCTIVE ENDOCRINOLOGY IN NORMAL PRE-MENOPAUSAL WOMEN

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ICI 182,780 has been found in vitro and in animal models to exert a pure anti-oestrogenic action with no agonist activity. 19 pre-menopausal women were prescribed 182,780, 12 mg intramuscularly, daily for 7 seven days prior to hysterectomy starting between day 5 to day 9 of the menstrual cycle, for benign gynaecological disease. 11 controls were also recruited. No significant adverse events were reported in either group. 3 women in the treatment group were withdrawn because of endocrine abnormalities or because they were in the luteal phase at the beginning of treatment. 12 of the 16 remaining treated women showed a consistent response to ICI 182,780 characterised by no increase in the plasma concentration of LH and FSH, no LH surge, continuing follicular growth ultrasonically, increasing plasma oestradiol concentrations, no increase in endometrial thickness and no ultrasonic evidence of ovarian hyperstimulation. The remaining 4 women showed an increase in endometrial thickness in parallel with an increase in plasma oestradiol concentration. Overall plasma oestradiol concentrations were significantly higher in the treated group compared with control group over the sampling interval. Pharmacodynamic data are being analyzed. Overall the results suggest that in a majority of pre-menopausal women ICI 182,780, 12 mg daily for 7 days does not stimulate gonadotrophin secretion and will suppress endometrial growth in spite of continuing oestradiol stimulation. The absence of adverse events or of evidence of ovarian hyperstimulation suggests that this compound may be able to be used for the treatment of oestrogen dependent diseases in pre-menopausal women.

P184 COMPARISONS OF THE BIOACTIVITY OF FEMALE RAT PITUITARY AND PLASMA LH

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Pituitary and plasma LH possess different physico-chemical characteristics (1). We have now compared their bioactives "in vitro", investigating their ability to stimulate the production of testosterone, progesterone and tissue plasminogen activator (tPA).

Pituitaries (n=9) and plasma (n=7) were collected on proestrus, the former were homogenised in buffer and the supernatant diluted 1:500. All samples were assayed by radioimmunoassay (RIA;NIH-RP3 standard) and the mouse Leydig cell bioassay. Samples were incubated for 48 hours with cultured granulosa cells isolated from rat ovarian follicles (≥400 μM diameter) and then the culture medium was assayed for progesterone by RIA. Samples were also incubated for 48 hours with SV40 transected human umbilical vein endothelial cells (SGHEC7) and the incubate assayed for total tPA by Elisa.

Results standardised to the concentration of steroid or tPA produced per ng of immunogenic LH showed that the ratio of plasma to pituitary activity was 4.1:1 for testosterone production; 3.8:1 for progesterone production, while for tPA, plasma LH produced 107±16.5 ng/ml/ng LH (n=7) but pituitary LH applied to the cells at 4.9±0.2 ng (n=9) was inactive.

These findings indicate that on release of LH from the pituitary gland into the circulation, there is a 4-fold increase in steroidogenic activity of LH, and also an increase in it's ability to produce tPA

1. Leigh, A.J., Chapman, A.J. & Wilson, C.A. J. Reprod. Fertil. Abstract Series 3. No 115 (1989).