Journal of Reproduction and Fertility (1993) **98**, 307–312

Effects of onapristone, tamoxifen and ICI 182780 on uterine prostaglandin production and luteal function in nonpregnant guinea-pigs

N. L. Poyser

Department of Pharmacology, University of Edinburgh Medical School, 1 George Square, Edinburgh EH8 9JZ, UK

Onapristone (a progesterone antagonist) or ICI 182780 (an oestrogen antagonist) administered to guinea-pigs on days 11–14 of the cycle significantly reduced uterine $PGF_{2\alpha}$ output on day 15. Concentrations of progesterone in plasma of onapristone-treated and ICI 182780-treated guinea-pigs were still high on day 15 indicating that luteal regression had been prevented. These findings indicate that progesterone and oestradiol are necessary for increased $PGF_{2\alpha}$ production by the uterus towards the end of the cycle, and support the hypothesis that oestradiol acting on a progesterone-primed uterus is the physiological stimulus for increased uterine $PGF_{2\alpha}$ synthesis and release in guinea-pigs. The capacity of the endometrium to synthesize $PGF_{2\alpha}$ on day 15 was reduced by treatment with ICI 182780 and, unexpectedly, by treatment with onapristone, indicating that onapristone may also be antagonizing the release or action of oestradiol in some way. Tamoxifen was an agonist in guinea-pigs since it induced vaginal opening. It had no inhibitory effect on uterine $PGF_{2\alpha}$ output and did not delay luteal regression when administered between days 11 and 14 of the cycle. However, it redirected PG synthesis in homogenates of endometrium and myometrium from PGI_2 (as indicated by 6-keto-$PGF_{1\alpha}$) to $PGF_{2\alpha}$. The output of 6-keto-$PGF_{1\alpha}$ from the uterus of day 15 guinea-pigs was reduced following tamoxifen treatment, but the high output of $PGF_{2\alpha}$ from the uterus was not affected.

Introduction

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) produced by the uterus is responsible for regression of the corpora lutea in the ovary of guinea-pigs (see Horton and Poyser, 1976; Poyser, 1981). Oestradiol administered to ovariectomized guinea-pigs maintained on progesterone stimulates uterine $PGF_{2\alpha}$ output (Blatchley and Poyser, 1974; Poyser, 1983a). During the oestrous cycle, oestradiol secretion from the ovary increases from day 10 (Joshi *et al.*, 1973); this precedes the increase in $PGF_{2\alpha}$ secretion from the uterus by 24 h (Blatchley *et al.*, 1972; Earthy *et al.*, 1975; Antonini *et al.*, 1976). Oestradiol acting on a progesterone-primed uterus therefore appears to be the physiological stimulus for increased $PGF_{2\alpha}$ production by guinea-pig uterus (particularly the endometrium) towards the end of the oestrous cycle, especially as oxytocin has no stimulatory effect on endometrial $PGF_{2\alpha}$ synthesis in guinea-pigs (Poyser and Brydon, 1983; Riley and Poyser, 1987). If this is so, appropriate steroid receptor antagonists should prevent the stimulation of uterine $PGF_{2\alpha}$ synthesis and release towards the end of the cycle, and thereby should delay luteal regression. Consequently, the effects of onapristone (a progesterone antagonist), tamoxifen and ICI 182780 (oestrogen antagonists) on uterine $PGF_{2\alpha}$ production and luteal function in guinea-pigs were investigated.

Materials and Methods

Twenty-five virgin guinea-pigs, weighing 650–850 g, were examined daily and a vaginal smear was taken when the vagina was perforate. Day 1 of the cycle was defined as the day preceding the post-ovulatory influx of leucocytes when cornification was at a maximum. All guinea-pigs had exhibited at least two cycles of normal duration (16 to 17 days) before being treated as described in the following experiments. The animals were killed by stunning and incising the neck on the day after the last day of treatment.

Experiment 1: effects of onapristone and tamoxifen

Guinea-pigs were injected s.c. once a day from days 11 to 14 of the cycle with 1 ml peanut oil containing 5% benzyl alcohol (control vehicle), 10 mg onapristone, or 10 mg tamoxifen (five animals per treatment). The uteri were removed on day 15. One uterine horn from each uterus was superfused with Krebs solution (5 ml min^{-1}; for composition see Mitchell *et al.*, 1977) at 37°C and pre-gassed with 5% CO_2–95% O_2. Samples of superfusate were collected for 10-min periods between 0–10 and 60–70 min of superfusion. The other uterine horn was divided into endometrium and myometrium by cutting away small pieces of endometrium from the myometrium. This tech-

Krebs solution and were incubated at 37°C for 60 min. After superfusion or incubation, the pH of the samples of superfusates and of the incubates were lowered to 4.0 with 1 mol HCl l^{-1}, and the PGs were extracted by shaking twice with ethyl acetate (50 and 20 ml for the superfusates and incubates, respectively). The two ethyl acetate extracts obtained from each sample were combined and evaporated to dryness at 50°C on a rotary evaporator. The recoveries of $PGF_{2\alpha}$ and PGE_2 are >90% and the recovery of 6-keto-$PGF_{1\alpha}$ is >80% by this method (Poyser and Scott, 1980; Swan and Poyser, 1983). The results are not corrected for recovery. The amounts of $PGF_{2\alpha}$, PGE_2 and 6-keto-$PGF_{1\alpha}$ present in each sample were measured by radioimmunoassay using antibodies raised in this laboratory; the crossreactivities have been reported elsewhere (Poyser, 1987). The inter- and intra-assay coefficients of variation were <11.8%. The detection limit was 10–30 pg per assay tube.

At the time of removing the uterus, a sample of peripheral blood was collected into a heparinized (20 U ml^{-1}) syringe. The blood was centrifuged at 2500 *g* for 15 min, and the plasma was withdrawn and stored at −20°C. Progesterone in the plasma samples was measured as described by Poyser and Horton (1975), using an antibody raised in this laboratory; the cross-reactivities have been reported elsewhere (Poyser, 1983b, 1984). The intra-assay coefficient of variation was 9.5%, and all the samples were measured in one assay. The detection limit was 40 pg per assay tube.

Experiment 2: effects of ICI 182780

Guinea-pigs were injected s.c. once a day from days 11 to 14 of the cycle with 0.8 ml 5% benzyl alcohol in peanut oil alone (controls) or containing 4 mg ICI 182780 (five animals per group). The uteri were removed on day 15 and treated as in Expt 1. The amounts of $PGF_{2\alpha}$, PGE_2 and 6-keto-$PGF_{1\alpha}$ present in the extracts obtained were measured by radioimmunoassay. The inter- and intra-assay coefficients of variation were <12%, and the detection limits were 20–30 pg PG per assay tube.

Progesterone was measured in a peripheral plasma sample, obtained from each guinea-pig at the time of removing the uterus, by radioimmunoassay as outlined in Expt 1. The intra-assay coefficient of variation was 10.1%, and all the samples were measured in one assay. The detection limit was 40 pg per assay tube.

Statistical tests

Results were analysed by the Student's *t* test or, if the variances of the two groups were significantly different by the variance ratio *F* test, by a modified *t* test for unequal variances (see Steel and Torrie, 1980).

Results

$PGF_{2\alpha}$ was the major PG released, together with lesser quantities of PGE_2 and 6-keto-$PGF_{1\alpha}$, from the uterus superfused *in vitro* from day 15 control guinea-pigs. These outputs of PGF

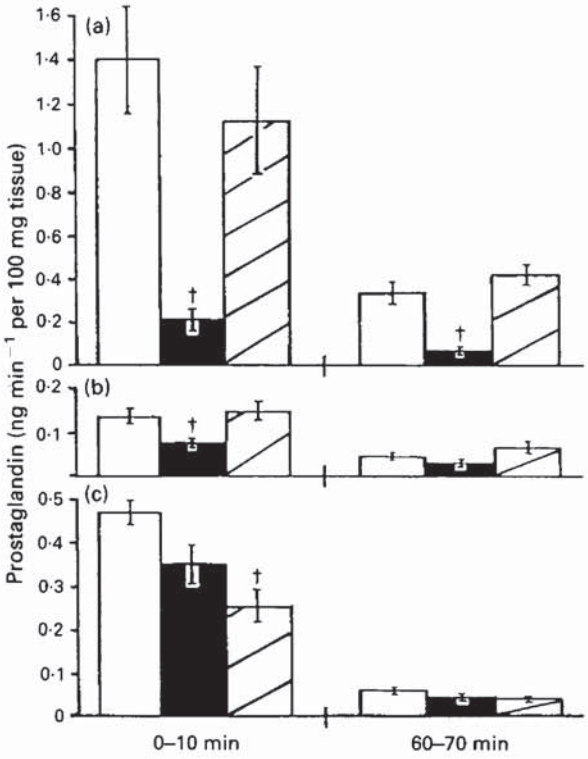

Fig. 1. Mean (±SEM, $n = 5$) outputs of (a) $PGF_{2\alpha}$, (b) PGE_2 and (c) 6-keto-$PGF_{1\alpha}$ from the day 15 uterus of (□) control, (■) onapristone-treated and (▨) tamoxifen-treated guinea-pigs when superfused *in vitro* during the periods (i) 0–10 min and (ii) 60–70 min. †Significantly ($P < 0.05$) lower than the control output of the same PG during the same period.

the first (0–10 min) and second (60–70 min) periods of superfusion (Figs 1 and 2). The treatment of guinea-pigs with onapristone between days 11 and 14 of the cycle significantly ($P < 0.05$) reduced the outputs from the uterus of $PGF_{2\alpha}$ on day 15 during both periods of superfusion, and of PGE_2 during the first period of superfusion. Onapristone had no significant effect on the output of 6-keto-$PGF_{1\alpha}$ during either superfusion period (Fig. 1). Tamoxifen administered to guinea-pigs between days 11 and 14 of the cycle had no effect on the uterine outputs on day 15 of $PGF_{2\alpha}$ and PGE_2, but significantly ($P < 0.05$) reduced the output of 6-keto-$PGF_{1\alpha}$ during the first but not the second period of superfusion (Fig. 1).

The treatment of guinea-pigs with ICI 182780 on days 11 to 14 of the cycle significantly ($P < 0.05$) reduced the outputs of $PGF_{2\alpha}$ and PGE_2 from the day 15 uterus during both periods of superfusion. ICI 182780 treatment had no effect on the output of 6-keto-$PGF_{1\alpha}$ from the day 15 uterus during either period of superfusion (Fig. 2).

$PGF_{2\alpha}$ and 6-keto-$PGF_{1\alpha}$ were the major PGs synthesized by homogenates of day 15 endometrium and myometrium, respectively, although the endometrium also synthesized significant quantities of 6-keto-$PGF_{1\alpha}$. PGE_2 was synthesized in smaller quantities by both tissues (Figs 3 and 4). Onapristone administered between days 11 and 14 of the cycle significantly ($P < 0.05$) reduced the amount of $PGF_{2\alpha}$ synthesized by homogenates of the day 15 endometrium without significantly

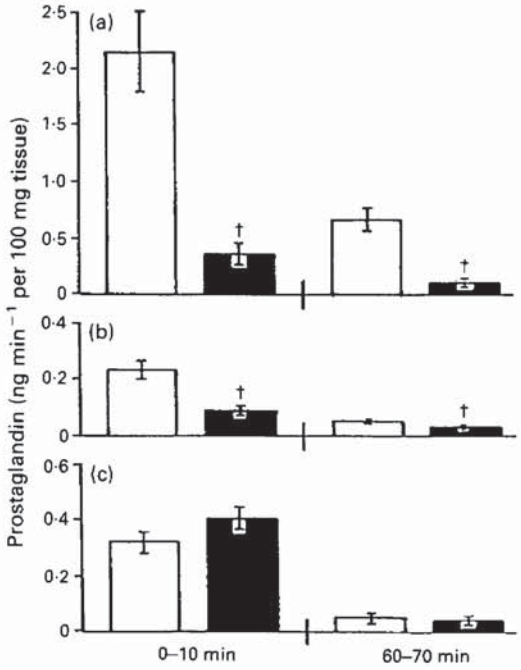

Fig. 2. Mean (±SEM, $n = 5$) amounts of (a) $PGF_{2\alpha}$, (b) PGE_2 and (c) 6-keto-$PGF_{1\alpha}$ from the day 15 uterus of (□) control and (■) ICI 182780-treated guinea-pigs when superfused *in vitro* during the periods (i) 0–10 min and (ii) 60–70 min. †Significantly ($P < 0.05$) lower than the control value for the same PG during the same time period.

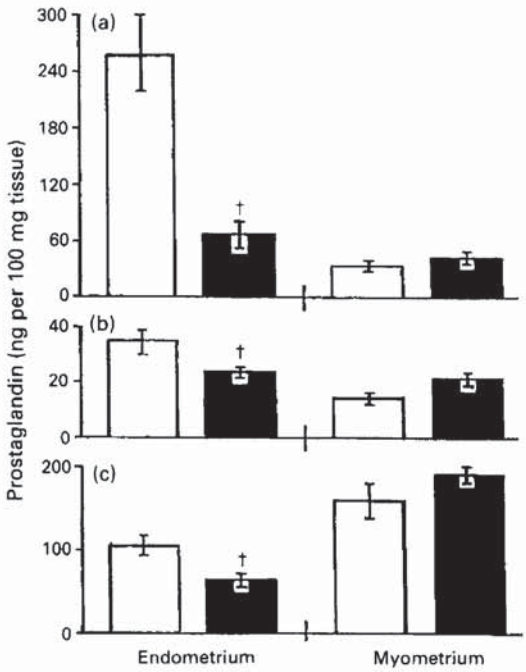

Fig. 4. Mean (±SEM, $n = 5$) amounts of (a) $PGF_{2\alpha}$, (b) PGE_2 and (c) 6-keto-$PGF_{1\alpha}$ synthesized during 1 h by homogenates of endometrium and myometrium from (□) control and (■) ICI 182780-treated guinea-pigs on day 15 of the cycle. †Significantly ($P < 0.05$) lower than the control value for the same PG in the same tissue.

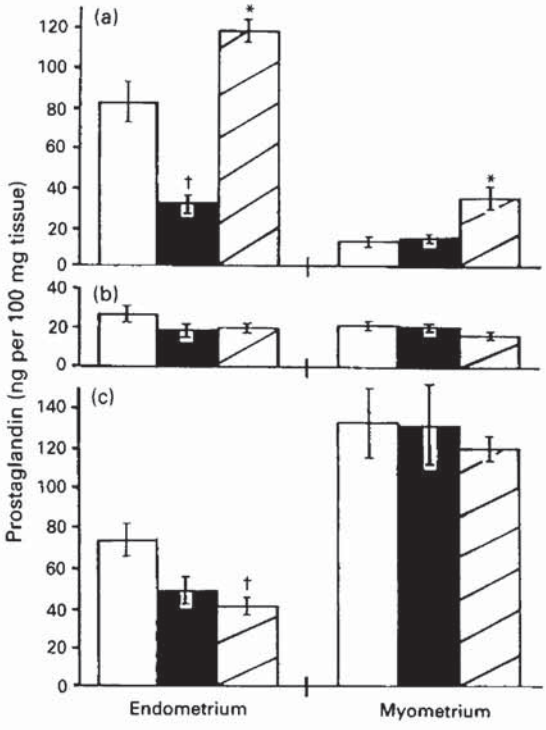

Fig. 3. Mean (±SEM, $n = 5$) amounts of (a) $PGF_{2\alpha}$, (b) PGE_2 and (c) 6-keto-$PGF_{1\alpha}$ synthesized during 1 h by homogenates of day 15 endometrium and myometrium from (□) control, (■) onapristone-treated and (▨) tamoxifen-treated guinea-pigs. †Significantly ($P < 0.05$) lower than the control value for the same PG in the same tissue.

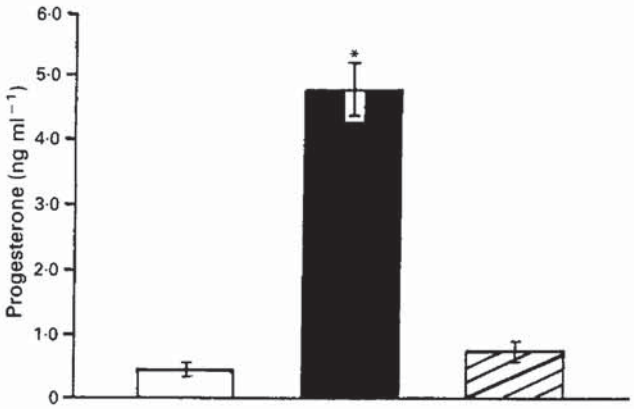

Fig. 5. Mean (±SEM, $n = 5$) concentrations of progesterone in the peripheral plasma of (□) control, (■) onapristone-treated and (▨) tamoxifen-treated guinea-pigs on day 15 of the cycle. *Significantly ($P < 0.05$) higher than the control and tamoxifen-treated values.

(although the synthesis of both PGs tended to be reduced; Fig. 3). Onapristone treatment had no effect on the amounts of the three PGs synthesized by homogenates of day 15 myometrium (Fig. 3). Tamoxifen administered between days 11 and 14 of the cycle significantly ($P < 0.05$) increased the amount of $PGF_{2\alpha}$ synthesized and significantly ($P < 0.05$) decreased the amount of 6-keto-$PGF_{1\alpha}$ synthesized by homogenates of the day 15 endometrium, without affecting PGE_2 synthesis (Fig. 3). Tamoxifen administration significantly ($P < 0.05$) increased the

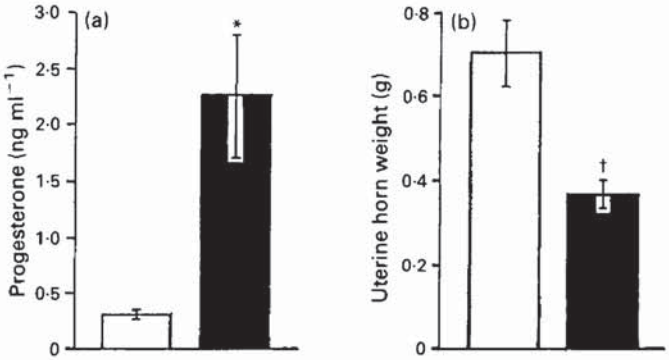

Fig. 6. Mean (±SEM, $n = 5$) (a) concentrations of progesterone in peripheral plasma, and (b) uterine horn weight in (□) control and (■) ICI 182780-treated guinea-pigs on day 15 of the cycle. *Significantly ($P < 0.05$) higher than the corresponding control value. †Significantly ($P < 0.05$) lower than the corresponding control value.

PGE_2 and 6-keto-$PGF_{1\alpha}$ synthesized (although these were slightly depressed).

Treatment with ICI 182780 from days 11 to 14 of the cycle significantly ($P < 0.05$) reduced the amounts of $PGF_{2\alpha}$, PGE_2 and 6-keto-$PGF_{1\alpha}$ synthesized by homogenates of the day 15 endometrium, with $PGF_{2\alpha}$ synthesis being particularly affected (Fig. 4). ICI 182780 treatment had no significant effect on the amounts of $PGF_{2\alpha}$, PGE_2 and 6-keto-$PGF_{1\alpha}$ synthesized by homogenates of day 15 myometrium (Fig. 4).

Concentrations of progesterone in peripheral plasma were typically low (< 1 ng ml^{-1}) on day 15 in control and tamoxifen-treated guinea-pigs, but were significantly ($P < 0.05$) increased in guinea-pigs treated with onapristone and ICI 182780 (Figs 5 and 6a). Tamoxifen caused the vagina to open after 2–3 days of treatment, which is in agreement with a previous report (Furr and Jordan, 1984).

Mean (±SEM, $n = 5$) uterine horn weights of the guinea-pigs used in Expt 1 were 0.662 ± 0.094, 0.509 ± 0.018, and 0.636 ± 0.022 g in the control, onapristone-treated, and tamoxifen-treated animals, respectively. These values did not differ significantly. In Expt 2, the uterine horn weight was significantly ($P < 0.05$) lower in ICI 182780-treated guinea-pigs than in control guinea-pigs (Fig. 6b).

Discussion

If oestradiol acting on a progesterone-primed uterus is the physiological stimulus for increasing uterine $PGF_{2\alpha}$ synthesis and release in guinea-pigs, inhibiting the effect of each steroid with a receptor antagonist should reduce uterine $PGF_{2\alpha}$ output and delay luteal regression. Onapristone (a progesterone antagonist) administered to guinea-pigs between days 11 and 14 of the cycle inhibited uterine $PGF_{2\alpha}$ output and extended luteal lifespan (as indicated by peripheral plasma progesterone concentrations) when examined on day 15. Consequently, endogenous progesterone appears to be essential for the increase in uterine $PGF_{2\alpha}$ synthesis and release after day 11 of the cycle. However, since maximum uterine $PGF_{2\alpha}$ output occurs when plasma progesterone concentrations are at their lowest, this inverse correlation supports a 'priming role' for (which indicates that PGE_2 may be a by-product of $PGF_{2\alpha}$ synthesis), but had no significant effect on 6-keto-$PGF_{1\alpha}$ output. This is in agreement with previous findings (Riley and Poyser, 1987, 1990) which showed that endometrial $PGF_{2\alpha}$ and PGI_2 (as indicated by 6-keto-$PGF_{1\alpha}$) syntheses are controlled independently.

The decrease in uterine $PGF_{2\alpha}$ output induced by onapristone is not due to increased PG metabolism, since the increases in peripheral plasma concentrations of 13,14-dihydro-15-keto-$PGF_{2\alpha}$ in guinea-pigs towards the end of the cycle (and which are indicative of increased uterine $PGF_{2\alpha}$ secretion) are prevented by onapristone treatment. Luteal function is also prolonged (Qing *et al.*, 1989).

During the cycle, the amounts of $PGF_{2\alpha}$ synthesized by homogenates of guinea-pig endometrium increase 2.2-fold between days 7 and 13 of the cycle as ovarian oestradiol output increases, but this increase reaches 4.4-fold at the end of the cycle after plasma progesterone concentrations have fallen (Poyser, 1983b). In ovariectomized guinea-pigs, oestradiol administered alone increases endometrial $PGF_{2\alpha}$ synthesizing capacity 3.2-fold, but when progesterone treatment precedes oestradiol administration the capacity of the endometrium to synthesize $PGF_{2\alpha}$ increases only 1.7-fold (Poyser, 1983b). These differences are not due to changes in PG metabolism since, in the absence of NAD^+, metabolism of PGs by the guinea-pig uterus is low (<5%; Poyser, 1979), nor are they due to lack of arachidonic acid since, during the homogenization process, large amounts of free arachidonic acid are released (Mitchell *et al.*, 1977). As prostaglandin endoperoxide synthase exhibits a self-catalysed destruction during the synthesis of PGs within the period studied (Lands *et al.*, 1973), the increases in the amounts of $PGF_{2\alpha}$ synthesized by homogenates of guinea-pig endometrium during the cycle or following oestradiol treatment are due to an increase in the amounts of enzymes that synthesize PGs that are present. Oestradiol stimulates the synthesis of these enzymes, but progesterone attenuates this stimulatory effect. However, oestradiol acting on a progesterone-primed uterus stimulates endometrial synthesis and release from the intact tissue, so this increase is not directly due to an increase in the amounts of $PGF_{2\alpha}$ synthesizing enzymes present in the endometrium. Consequently in the present study, whereas onapristone prevents the stimulation of endometrial $PGF_{2\alpha}$ synthesis and secretion, it might be expected to increase the amounts of enzymes that synthesize $PGF_{2\alpha}$ in the endometrium as the attenuating effect of progesterone on this stimulatory action of oestradiol should be prevented. However, this did not occur since onapristone treatment reduced the amounts of $PGF_{2\alpha}$ synthesized by the day 15 endometrial homogenates by 68%. The amounts of PGE_2 and 6-keto-$PGF_{1\alpha}$ synthesized by homogenates of day 15 endometrium following onapristone treatment tended also to be reduced, so that in these animals the total amount of $PGF_{2\alpha}$, PGE_2 and 6-keto-$PGF_{1\alpha}$ synthesized by endometrial homogenates was reduced by 50%.

It would seem that onapristone may also be inhibiting the action of oestradiol either by reducing ovarian oestradiol output (possibly as a consequence of maintaining plasma progesterone concentrations at a high value), or by some action of onapristone on the uterus. Onapristone did not reduce the uterine horn weight of day 15 guinea-pigs, which suggests that it is not inhibiting the action of oestradiol directly (i.e. at the

oestradiol alone or with onapristone, there is a dose-dependent inhibition by onapristone of oestradiol-induced gland formation in the endometrium, and also degenerative changes occur in the glandular epithelial cells within the endometrium. These changes produced by onapristone appear to be mediated by progesterone receptors since the additional administration of progesterone prevents these actions of onapristone (Chwalisz *et al.*, 1991). Since many studies in a variety of species have indicated that the glandular epithelial cells are the main source of $PGF_{2\alpha}$ and are the cells acted upon by steroid hormones, and if similar inhibitory and degenerative changes affect glandular epithelial cells in the endometrium of guinea-pigs as in rabbits following onapristone treatment, this may explain why onapristone has an inhibitory effect on the amounts of $PGF_{2\alpha}$ synthesized by homogenates of the endometrium at the end of the cycle. However, as plasma concentrations of progesterone remained high in the onapristone-treated guinea-pigs and progesterone prevented the degenerative changes induced in rabbit endometrium by onapristone, another reason may have to be sought to explain why onapristone reduced the PG synthesizing capacity of guinea-pig endometrium. The mechanism by which onapristone reduces endometrial PG synthesizing capacity merits further study.

Tamoxifen was an agonist in guinea-pigs as it induced vaginal opening within 2 to 3 days after the start of treatment, and it did not decrease uterine weight. Tamoxifen had no inhibitory effect on uterine $PGF_{2\alpha}$ output, and did not prevent luteal regression from occurring at the normal time. Tamoxifen significantly increased the amounts of $PGF_{2\alpha}$ synthesized by homogenates of the endometrium and myometrium, and significantly reduced the amount of 6-keto-$PGF_{1\alpha}$ synthesized by homogenates of the endometrium. The amount of 6-keto-$PGF_{1\alpha}$ synthesized by homogenates of the myometrium also tended to be reduced after tamoxifen treatment. However, the total amounts of $PGF_{2\alpha}$, PGE_2 and 6-keto-$PGF_{1\alpha}$ synthesized by homogenates of endometrium and myometrium, respectively, did not differ between the control and tamoxifen-treated guinea-pigs. This indicates that tamoxifen switches uterine PG synthesis away from PGI_2 (as indicated by 6-keto-$PGF_{1\alpha}$) and towards $PGF_{2\alpha}$. Although there was a reduction in uterine 6-keto-$PGF_{1\alpha}$ output following tamoxifen treatment, there was no corresponding increase in $PGF_{2\alpha}$ output, although uterine $PGF_{2\alpha}$ synthesis and release was high.

The administration of ICI 182780 significantly reduced uterine horn weight by approximately 50%, indicating that ICI 182780 is an anti-oestrogen in guinea-pigs. The treatment of guinea-pigs with ICI 182780 between days 11 and 14 of the cycle significantly reduced uterine $PGF_{2\alpha}$ output when measured on day 15. Luteolysis was therefore prevented in ICI 182780-treated guinea-pigs as indicated by the high plasma progesterone concentrations. ICI 182780, like onapristone, also reduced PGE_2 output without significantly affecting the output of 6-keto-$PGF_{1\alpha}$. ICI 182780 treatment also prevented the increase in endometrial $PGF_{2\alpha}$ synthesizing capacity normally observed by day 15 of the cycle, which agrees with the hypothesis that this increase is under the control of endogenous oestradiol (Poyser, 1983b). The amounts of PGE_2 and 6-keto-$PGF_{1\alpha}$ synthesized by homogenates of day 15 endometrium were also reduced by ICI 182780, but the extents of these reductions were not as large as for PGF$_{2\alpha}$. This indicates that it is endometrial PGF

of $PGF_{2\alpha}$, PGE_2 and 6-keto-$PGF_{1\alpha}$ synthesized by homogenates of myometrium were unaffected by treatment with ICI 182780. Thus, PG production by the myometrium is apparently not controlled by oestradiol.

Overall, the findings with onapristone and ICI 182780 indicate that endogenous progesterone and oestradiol are necessary for the stimulation of uterine $PGF_{2\alpha}$ synthesis and secretion, and they support the hypothesis that oestradiol acting on a progesterone-primed uterus is the stimulus for increased $PGF_{2\alpha}$ production by the endometrium. Surprisingly, onapristone, like ICI 182780, reduced the amounts of $PGF_{2\alpha}$ synthesized by homogenates of the endometrium, but not of the myometrium, which suggests that in some way onapristone is also inhibiting the release or the action of oestradiol. Tamoxifen proved to be an agonist in guinea-pigs, so it had no inhibitory effect on uterine $PGF_{2\alpha}$ synthesis and release. However, tamoxifen did reduce uterine 6-keto-$PGF_{1\alpha}$ synthesis apparently by causing a switch to $PGF_{2\alpha}$ synthesis. The treatment with a pure oestrogen receptor antagonist may be beneficial in preventing an increase in uterine PG production when such an increase is not desirable, e.g. (i) in early pregnancy in non-primate mammalian species when uterine $PGF_{2\alpha}$ synthesis has not been suppressed sufficiently so that luteal function is inadequate (see Poyser, 1981), and (ii) in disorders of menstruation such as dysmenorrhoea (Lundström *et al.*, 1976). Progesterone receptor antagonists may also have a similar use in menstrual disorders.

The technical assistance of L. Marshall is much appreciated. This study was supported by a grant from The Wellcome Trust. Onapristone was a generous gift from Schering AG, Berlin, Germany, and tamoxifen and ICI 182780 were generous gifts from ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK.

References

Antonini R, Turner TT and Pauerstein CJ (1976) The hormonal control of the guinea-pig corpus luteum during early pregnancy *Fertility and Sterility* **27** 1322–1325

Blatchley FR and Poyser NL (1974) The effect of oestrogen and progesterone on the release of prostaglandins from the uterus of the ovariectomised guinea-pig *Journal of Reproduction and Fertility* **40** 205–209

Blatchley FR, Donovan BT, Horton EW and Poyser NL (1972) The release of prostaglandins and progestin into the utero–ovarian venous blood of guinea-pigs during the oestrous cycle and following oestrogen treatment *Journal of Physiology* **222** 69–88

Chwalisz K, Hegel-Hartung C, Fritzemeier KH, Beier HM and Elger W (1991) Inhibition of the estradiol-mediated endometrial gland formation by the anti-gestagen onapristone in rabbits – relationship to uterine estrogen receptors *Endocrinology* **129** 312–322

Earthy M, Bishop C and Flack JD (1975) Progesterone and prostaglandin F concentrations in utero–ovarian venous plasma of cyclic guinea-pigs *Journal of Endocrinology* **64** 11P–12P

Furr BJA and Jordan VC (1984) The pharmacology and clinical uses of tamoxifen *Pharmacology and Therapeutics* **25** 127–205

Horton EW and Poyser NL (1976) Uterine luteolytic hormone: a physiological role for prostaglandin $F_{2\alpha}$ *Physiological Reviews* **55** 595–651

Joshi HS, Watson DJ and Labhsetwar AD (1973) Ovarian secretion of oestradiol, oestrone, 20-dihydroprogesterone and progesterone during the oestrous cycle of the guinea-pig *Journal of Reproduction and Fertility* **35** 177–182

Lands WEM, LeTellier PR, Rome LH and Vanderhoek JY (1973) Inhibition of prostaglandin synthesis *Advances in the Biosciences* Vol. 9, pp 15–28 Ed. S Bergström. Pergamon Press, Braunschweig

Leaver HA and Poyser NL (1981) Distribution of arachidonic acid and other

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.