The effect of intra-aortic prostaglandin F-2α on uterine motility in pregnant goats

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Summary. Aortic infusions of PGF-2α to goats during late pregnancy had no dramatic effects on uterine motility. Only when plasma progesterone concentrations had decreased by 50% due to the luteolytic action of PGF-2α did uterine activity increase. No cervical softening was detected during the infusion periods. Cervical softening was detected after the decline in progesterone concentration and the increases in endogenous PGF and uterine motility. It is suggested that the corpus luteum, presumably by secretion of progesterone, has an inhibitory action on the cervix, preventing other hormones from inducing dilatation.

Introduction

Removal of the corpus luteum (CL) from pregnant goats causes an abrupt decrease in uterine venous plasma progesterone concentrations, a rapid increase in the concentration of PGF 24 h later, before or coincident with cervical softening, and abortion after a consistent interval of 30 h (Cooke, Knifton & Ward, 1975). Aortic infusions of PGF-2α at 20 µg/min after such luteectomy significantly increased uterine motility, and shortened the time to cervical effacement but did not change the time to abortion (Cooke, Knifton, Fitzpatrick & Ward, 1977).

These infusion experiments have been repeated in late pregnant goats to observe any effect of the CL on the response of the uterus to PGF-2α.

Materials and Methods

The 3 goats used were 124–129 days after mating; each carried twin fetuses. An intrauterine pressure-recording balloon (27 x 5 mm: Portex Ltd), intra-aortic infusion cannula and uterine venous sampling cannula were introduced into each animal under general anaesthesia as previously described (Cooke et al., 1977). PGF-2α (Prostin F-2α: Upjohn Ltd) was infused for three 3-h periods at a rate of 20 µg/min, beginning 3–5 h after surgery when the animals were conscious and able to stand; each infusion was separated by a 3-hour interval.

All hormones were estimated by specific radioimmunoassay; PGF (i.e. PGF-1α and PGF-2α) according to a modified version of that described by Sharma (1972) and progesterone, oestrone, oestradiol-17α and oestradiol-17β according to the method of Hotchkiss, Atkinson & Knobil (1971). The specificities and cross-reactions of the anti-sera used have been reported (Sharma, 1972; Furr, 1973; Dobson & Dean, 1974). Assaying a plasma sample of low hormone concentration, the respective inter- and intra-assay coefficients of variation were 8·6 (n = 7) and 5·3% (n = 10) for PGF, 3·9 (n = 5) and 8·5% (n = 20) for progesterone, 12·9 (n = 6) and 15·3% (n = 10) for oestrone, 7·0 (n = 8) and 9·7% (n = 10) for oestradiol-17α, and 8·4 (n = 5) and 11·2% (n = 7) for oestradiol-17β. Assaying a plasma sample of high hormone concentration, the respective inter- and intra-assay coefficients of variation were 3·6 (n = 7) and 4·5% (n = 10) for PGF, 2·5 (n = 5) and 4·9% (n = 20) for progesterone, 9·7 (n = 6) and 13·3% (n = 10) for oestrone, 6·0 (n = 8) and 8·7% (n = 10) for oestradiol-17α, and 7·5 (n = 5) and 12·3% (n = 7) for oestradiol-17β.
concentration the respective inter- and intra-assay coefficients of variation were 10.6 (n = 10) and 6.0% (n = 10) for PGF, 4.1 (n = 5) and 3.8% (n = 10) for progesterone, 14.0 (n = 6) and 7.2% (n = 10) for oestrone, 7.7 (n = 8) and 5.1% (n = 10) for oestradiol-17a, and 10.6 (n = 6) and 5.0% (n = 7) for oestradiol-17β. The sensitivity of each assay was 18.1 pg for PGF, 4.1 pg for progesterone, 6.1 pg for oestrone, 9.8 pg for oestradiol-17a and 7.2 pg for oestradiol-17β.

Results for PGF are presented without correction for recovery which was, in goat plasma, 86.1 ± 6.3% (n = 40). Results for all steroids are corrected for recovery which was 69.8 ± 4.2% (n = 30) for progesterone; 81.4 ± 3.5% (n = 40) for oestrone; 82.9 ± 3.6% (n = 35) for oestradiol-17α and 82.5 ± 4.2% (n = 31) for oestradiol-17β.

Intrauterine pressure was recorded as previously described (Cooke et al., 1977). In all animals the cervix was palpated after each blood sample to assess consistency and to detect dilatation.

Data were analysed using Spearman’s Rank correlation coefficient, and are presented as mean ± s.d.

Results

Concentrations of PGF and steroids in uterine venous plasma in each goat are summarized in Text-fig. 1. The mean PGF concentration for the 3 goats during infusions was 5.11 ± 3.34 ng/ml (n = 41); this was significantly (P < 0.01) less than the mean concentration attained during infusions after luteotomy (Cooke et al., 1977). However, this was due to a leak in the infusion cannula in Goat 24 during the first two infusions. Plasma PGF concentrations were, nevertheless, comparable to those recorded during cervical dilatation in goats after luteotomy (Cooke et al., 1975). In all 3 goats concentrations of either oestrone or oestradiol-17α or both increased significantly (P < 0.05) after infusion 1 and before infusion 3, and preceded the rise in endogenous PGF. This increase in uterine venous plasma PGF was very gradual relative to that seen in lutectomized goats, taking place over 25 h rather than 6 h. All 3 goats aborted at a mean interval of 43.32 ± 6.24 h after the start of infusion 1 (0 h). This was significantly longer than the mean abortion time after CL removal, with (Cooke et al., 1977) or without (Cooke et al., 1975) PGF-2α infusions.

No immediate uterine response was observed to the first two PGF-2α infusions, and uterine activity began at 1.0, 0.5 and 2.0 h after the start of infusion 2; contractions were of very low amplitude (1–2 mmHg) and irregular frequency (4–10/10 min). Plasma progesterone concentrations had fallen by 46.53 ± 4.76% (n = 3) of pre-infusion values. There was a brief uterine hypertonus in all 3 goats 5–16 min after the start of the 3rd infusion, but when this was assessed in terms of Montevideo units (product of mean amplitude and number of contractions in 10 min: Caldeyro-Barcia et al., 1957), there was an increase (2-fold) of activity in Goat 24 only.

No cervical changes were detected during the periods of PGF-2α infusions. Cervical softening was detected at 10 h (Goat 21), 14 h (Goat 22) and 11 h (Goat 24) before delivery.

Discussion

These results confirm that onset of myometrial activity in the goat is temporally related to a decline in plasma progesterone concentration, as previously reported (Umo, Fitzpatrick & Ward, 1976; Jones & Knifton, 1977). In this study the presence of the corpus luteum inhibited the response of the uterus to exogenous PGF-2α; effective uterine contractions only developed after plasma progesterone concentrations had fallen, presumably in response to the luteolytic effect of PGF-2α. Conclusive evidence of a direct causal interaction between reduced plasma progesterone concentrations and uterine motility induced by exogenous PGF-2α would require further experiments involving administration of progesterone to luteectomized goats.
**Text-fig. 1.** Uterine venous plasma concentrations of progesterone (O), PGF (●), oestrone (△), oestradiol-17α (□) and oestradiol-17β (▲) in 3 goats infused (horizontal bars) with 20 μg PGF-2α/min via the aorta: 0 h is the start of the first infusion. Surgery was performed during the period marked by the hatched bar. A = abortion of wins (in all 3 goats); M = onset of uterine activity; S = first detectable cervical softening.
Myometrial activity developed in all goats despite the failure of plasma progesterone concentrations to fall below 3–5 ng/ml at abortion. This suggests that in the goat, as reported for the rat (Csapo & Wiest, 1969) and rabbit (Challis, Porter & Ryan, 1974), there is some critical level of plasma progesterone concentration below which uterine activity develops. This contrasts with the findings of Jones & Knifton (1977) who observed a significant (P < 0.01) correlation between increasing uterine activity and the decline in plasma progesterone concentrations over the last 7 days of pregnancy. Umo et al. (1976), however, only observed an increase in uterine activity over the last 24 h of pregnancy when plasma progesterone concentrations had fallen to about 2 ng/ml.

The results of this study, in conjunction with previous infusion experiments (Cooke et al., 1977), suggest that progesterone from the corpus luteum has an inhibitory action on the cervix, preventing other hormones from inducing dilatation, as previously postulated for the rat (Hollingsworth, Isherwood & Forster, 1979) and goat (Fitzpatrick, 1977). Administration of progesterone to lutectomized pregnant goats inhibits both the onset of uterine motility and cervical effacement (R. G. Cooke & A. Knifton, unpublished data). In goats induced to kid by Cloprostenol treatment (a PGF-2α analogue) cervical softening only occurred when progesterone concentrations had fallen considerably (Fitzpatrick & Dobson, 1979). The effect of PGF-2α on the cervix might therefore be indirect through producing progesterone withdrawal and increasing uterine activity. However, quantitative measurements of cervical extensibility, such as those used by Hollingsworth et al. (1979), rather than the subjective assessment employed in the present study, are required to substantiate this.

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References


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