Stimulation of uterine activity by administration of prostaglandin F-2 α during parturition in sheep

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In sheep, prostaglandin (PG) F-2 α concentrations rise in uterine venous plasma and in myometrium and maternal cotyledons before dexamethasone-induced parturition (Liggins & Grieves, 1971). As in many other species these high PGF-2 α concentrations are thought to play a role in stimulating uterine contractions (Thorburn, Nicol, Bassett, Shutt & Cox, 1972). The experimental evidence to date does not support an acute effect of PGF-2 α in the pregnant ewe (Liggins, Grieves, Kendall & Knox, 1972; Oakes, Mofid, Brinkman & Assali, 1973; Keirse *et al.*, 1973). However, a positive effect of chronic PGF-2 α administration on uterine contractility has been reported (Liggins, Fairclough, Grieves, Kendall & Knox, 1973); in this case the myometrial sensitivity to oxytocin was greatly increased after PGF infusion for 12 hr and spontaneous uterine contractions were observed after 24 hr of treatment. This report describes experiments designed to determine whether PGF-2 α can exert an acute effect on uterine activity during parturition in sheep.

Aortic, amniotic, fetal and utero-ovarian venous catheters were established in 5 ewes between Days 128 and 137 of gestation. All animals gave birth to live lambs. Intra-fetal dexamethasone administration was used to induce parturition in 4 of these animals; in such ewes the endocrine changes are similar to those associated with spontaneous parturition at term (Liggins *et al.*, 1972; Thorburn *et al.*, 1972). Dexamethasone was infused at a rate of 1–3 mg/24 hr into the fetal vena cava through a catheter inserted via a tarsal vein. For these 4 animals the mean ($\pm$ S.D.) time from induction to parturition was 41 $\pm$ 9 hr. The fifth animal gave birth spontaneously on Day 144 of gestation. The concentrations of progesterone, total unconjugated oestrogens and PGF were measured by radioimmunoassays as previously described (Flint, Anderson, Patten & Turnbull, 1974; Mitchell, Flint & Turnbull, 1975). Serial infusions of PGF-2 α were performed via the maternal aorta, with PGF-2 α (THAM salt) being infused at a rate which resulted in uterine venous plasma PGF levels similar to those found previously at term (Table 1).

Table 1. Hormone levels in the utero-ovarian venous plasma of Ewe 1 during and 4 hr after (figures in parentheses) experiment

Exp.	Time before induced parturition (hr)	Progesterone (ng/ml)	Total unconjugated oestrogens (pg/ml)	PGF (ng/ml)
1	48	45.8 (43.0)	< 20 (20)	34
2	28	38.0 (31.0)	< 20 (20)	45
3	19	25.3 (15.6)	42 (120)	35
4	9	9.0 (10.7)	220 (306)	25
5	4	10.7 (8.3)	306 (400)	44

The response to intra-aortic infusion of PGF-2 α was similar in all 4 treated ewes (3 induced parturitions and one of natural onset). The results for one of these animals are shown in Plate 1 and Table 1. In the fifth animal the infusion catheter was inserted to a point posterior to the junction of the iliac and uterine arteries: infusion of PGF-2 α (125 μ g/min) in this animal and intra-aortic saline infusion in another produced no change in uterine contractility (results not shown). There were no changes in the concentrations of progesterone and total unconjugated oestrogens in uterine venous plasma samples taken during the first infusion in Ewe 1 (Plate 1). The pressure recordings were analysed

manually in terms of Montevideo units as defined by Caldeyro-Barcia *et al.* (1957), i.e. the product of intensity (rise in pressure in mmHg each contraction produces in the amniotic fluid) and frequency (number of contractions/10 min). The results for the total experimental period were averaged for comparison with the total control period. The amplitude of contraction was taken as the distance between peak and base of each contraction. Intrauterine pressure changes in response to PGF-2 α showed a characteristic pattern in all 4 treated animals, an initial hypertonus being followed by increased uterine contractility. Closer to parturition there was an apparent increase in response in all the ewes, the effect being both greater and longer lasting. There was a mean tenfold stimulation of uterine activity during the infusions compared to the relevant control periods ($P < 0.005$, one-tailed *t* test).

The immediate effect of PGF-2 α on uterine activity may have been missed by previous investigators because too low a dose was given. From this study it appears that, apart from an indirect effect on the ovine myometrium by a lowering of the oxytocic threshold, PGF-2 α can also exert an acute effect on uterine contractility. This is consistent with the idea that the surge of PGF-2 α at term is the final impetus for fetal expulsion in the sheep.

We are grateful to Dr B. J. Furr, I.C.I. Pharmaceuticals Division, Alderley Park, Cheshire, Dr K. J. Thrower, Upjohn Ltd, Crawley, Sussex and Dr K. T. Kirton, Upjohn Ltd, Kalamazoo, Michigan, U.S.A. for gifts of antisera and prostaglandin standards. We also thank Professor G. S. Dawes for animal facilities, and the M.R.C. for a Studentship to M. D. M. and Grant No. G971/809/C.

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Received 23 February 1976

Intra-amniotic pressure recordings during five experiments in Ewe 1, which gave birth to twin lambs 53 hr after the start of intra-fetal dexamethasone infusion. Intra-aortic infusion of PGF-2 α at 94 μ g/min began at A and ended at B. The pattern of contractility shown before starting PGF-2 α infusion was typical of that observed during the preceding 30 min.