Increasing uterine response to vaginal distension during late pregnancy in sheep

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Summary. Intrauterine pressure changes were monitored in 5 pregnant ewes and uterine venous prostaglandin (PG) F concentrations were determined after distension of the vagina. Uterine contractility and utero-ovarian PGF concentrations were elevated by vaginal distension and the magnitude of both effects increased as parturition approached.

Introduction

The 'Ferguson Reflex', enhanced uterine contractility after stretching of the cervix and vagina of puerperal rabbits (Ferguson, 1941), occurs in sheep. Oxytocin is the humoral component of the reflex and its circulating level rises within 1 min of vaginal distension in cyclic and lactating sheep (Roberts & Share, 1968; Debackere, Peeters & Tuytens, 1961). Vaginal distension in pregnant sheep results in elevated uterine venous prostaglandin (PG) F levels (Flint, Anderson, Patten & Turnbull, 1974) and a surge of oxytocin during vaginal distension precedes this elevation (Flint, Forsling, Mitchell & Turnbull, 1975). To determine whether the Ferguson Reflex is enhanced before the onset of parturition we performed serial vaginal distensions on sheep in late pregnancy and monitored intra-amniotic pressure changes, while taking uterine venous blood samples for PGF estimations.

Materials and Methods

Five ewes of the Dorset, Suffolk and Border Leicester breeds were used and gestational ages at operation for insertion of utero-ovarian venous and amniotic catheters by the methods described by Flint *et al.* (1974) ranged from 123 to 132 days. In Ewe 3 a catheter was inserted into the fetal inferior vena cava via a tarsal vein. Ewe 2 gave birth spontaneously on Day 141 of gestation; the first fetus died during an obstructed birth, but the second fetus was born alive. All four other animals produced live lambs. Ewe 3 gave birth 44 h after the start of intrafetal infusion of dexamethasone (1 mg/24 h), and Ewes 1, 4 and 5 gave birth 33, 44 and 60 h, respectively, after intrafetal injection of dexamethasone (25 mg i.m.). The technique of dexamethasone induction of parturition (Liggins, 1968; Mati, Horrobin & Bramley, 1973) results in changes of progesterone, oestrogen and PGF concentrations comparable to those preceding the natural onset of parturition (Thorburn, Nicol, Bassett, Shutt & Cox, 1972; Liggins, Fairclough, Grieves, Kendall & Knox, 1973; Flint *et al.*, 1974). Vaginal distension was effected manually while the animals remained in metabolism cages. Blood samples were collected into ice-cold heparinized tubes and centrifuged within 1 h; plasma was stored at -20°C . Progesterone, total unconjugated oestrogens and PGF were measured by radioimmunoassays as described by Flint *et al.* (1974) and Mitchell *et al.* (1975).

Results

Sharma & Fitzpatrick (1974) showed that frequently repeated administration of oxytocin resulted in attenuated response of the uterus in terms of PGF output, and this effect is also seen after repeated

vaginal distension in late pregnancy (Text-figs 1a and 1b). For this reason vaginal distension was not repeated more than three times in any animal. As shown in Text-figs 1(c) and 1(d) the length of time for which the vagina was distended did not appear to alter substantially the responses measured.

The abdominal straining which occurs during vaginal distension (Text-figs 1 and 2) was a consistent finding and is characteristic of the second stage of parturition, as noted in the goat (Peeters, De Vos & Houvenaghel, 1971), but was unaffected by the endocrine status of the ewe. The 20 min after vaginal distension were considered as the experimental period and uterine activity was measured in terms of Montevideo units as defined by Caldeyro-Barcia *et al.* (1957). The increased uterine contractility following vaginal distension becomes marked close to parturition (Text-fig. 2) and may lead to rhythmic contractions (Text-fig. 2c). In Ewe 5 (Text-fig. 2) there was a 1.6-, 2.5- and 3.7-fold stimulation of uterine activity at 50, 31 and 15 h, respectively, before birth. In Ewe 3 there was no stimulation and a 1.5-fold stimulation of uterine activity at 41 and 14 h, respectively, before parturition. Ewe 4 showed a 1.3-fold stimulation at 37 h before and a 3.3-fold stimulation at 20 h before birth (pressure traces not shown). Increased contractility occurred for a variable time, but appeared to continue longer close to parturition (Text-fig. 2), sometimes not returning to prestimulation levels. Another feature of the intrauterine pressure changes was the variable uterine hypertonus occurring for approximately 5 min immediately after vaginal distension (see Text-fig. 1c especially).

The increases in response to vaginal distension were concurrent with falling levels of progesterone in maternal plasma (Table 1). No effects could be ascribed to rising oestrogen levels; as shown in Table 1 changes in uterine sensitivity preceded any large increases in oestrogens.

Table 1. Experimental details of sheep

Ewe	Time of birth	Time of exp. before birth	Utero-ovarian venous conc.	
			Progesterone (ng/ml)	Total unconjugated oestrogens (pg/ml)
1	33 h after	8 h	48	120
	dexamethasone	3.5 h	32	340
2	141 days <i>post coitum</i>	7 days	44.5	102
3	44 h after	41 h	55	54
	dexamethasone	14 h	26	100
4	44 h after	37 h	58	100
	dexamethasone	20 h	23.3	176
5	60 h after	50 h	18.5	60
	dexamethasone	31 h	3.6	180
		15 h	0.7	112

The time course of the rise in PGF concentrations in response to vaginal distension was similar to that found by Flint *et al.* (1975); peak levels 3–5 min from the beginning of vaginal distension fell to basal values within 30 min. Minimal changes in PGF concentrations were found 7 days before parturition (data not shown) or shortly after the start of dexamethasone treatment (Text-fig. 2d) and in Ewes 3 and 4 at 41 and 37 h, respectively, before birth (data not shown). As progesterone concentrations fell (Table 1), markedly elevated PGF concentrations were obtained in response to vaginal distension (Text-fig. 2d), and in Ewes 3 and 4 at 14 and 20 h, respectively, before birth there were 4- and 2-fold elevations of PGF concentrations in utero-ovarian venous plasma (data not shown).

Discussion

This work demonstrates an increasing uterine response to vaginal distension in terms of both contractility and plasma PGF concentrations. Of interest also are the two factors which do not change

Text-fig. 1. Effect of vaginal distension (horizontal bars) in Ewe 1 on intra-amniotic pressure (a, c) and prostaglandin F concentrations (b, d) at 8 h (a, b) and 3-5 h (c, d) before parturition. The control period of uterine activity was typical of that observed over the preceding 30 min.

Text-fig. 2. Effect of vaginal distension (horizontal bars) in Ewe 5 on intra-amniotic pressure (a, b, c) and utero-ovarian PGF concentrations (d) at 50 h (a, and ■ in d), 31 h (b, ●) and 15 h (c, ▲) before parturition. The control period of uterine activity was typical of that observed over the preceding 30 min.

in response to vaginal distension closer to parturition, i.e. the abdominal straining and the time course of increasing PGF levels. Abdominal straining occurs immediately vaginal distension commences and probably represents a reflex unaffected by the endocrine environment. This effect will presumably be of importance in the expulsion of the fetus. The time course of elevation of PGF concentrations is consistent with previous work (Flint *et al.*, 1975), but has now been shown not to be influenced by the hormonal changes associated with parturition. It has been shown that progesterone diminishes and oestrogen potentiates the release of oxytocin in response to vaginal distension (Roberts & Share, 1969) while the uterus also becomes increasingly sensitive to oxytocin during late gestation (Hindson, Schofield & Ward, 1969), perhaps due to rising basal levels of PGF, which lower the threshold for oxytocin stimulation (Liggins *et al.*, 1973). The increasing uterine activity following vaginal distension close to parturition, as progesterone concentrations fall and oestrogen concentrations rise, could therefore be explained by an increased reflex release of oxytocin acting on an increasingly sensitive uterus.

The increasing elevation of PGF concentrations in response to vaginal distension close to parturition might also be explained in terms of increased oxytocin secretion. In addition, however, it seems likely that uterine PGF output in response to oxytocin is potentiated near term since the same trend in PGF output has been noted in response to exogenous oxytocin administration (Mitchell *et al.*, 1975), when the quantity of oxytocin reaching the uterus is presumably not a limiting factor. The possibility that oxytocin affects uterine activity and PGF concentrations by separate mechanisms is supported by the finding that oxytocin can stimulate uterine activity in the presence of an inhibitor of PG synthesis which prevents a rise in plasma PGF concentrations (Roberts, Barcikowski, Wilson, Skarnes & McCracken, 1975).

Oxytocin levels are increased in men and women following administration of PGs (Gillespie, Brummer & Chard, 1972). If such an effect occurred in the sheep a spiral mechanism might be postulated whereby increasing quantities of myometrial stimulants could account for the rapid nature of parturition in this species. Such a self-accentuating mechanism would be quiescent at early stages of gestation, but would gradually mature to optimal efficiency at term, awaiting only the final 'trigger' of cervical and vaginal distension by the descending fetal presenting parts.

We thank Dr B. J. Furr, I.C.I. Pharmaceuticals Division, Alderley Park, Cheshire, and Dr K. J. Thrower, Upjohn Ltd, Crawley, Sussex, for gifts of antisera, and Professor G. S. Dawes for the use of the animal facilities at the Nuffield Institute for Medical Research. M.D.M. acknowledges the support of an M.R.C. Studentship. This work was supported by M.R.C. Programme Grant No. G 971/809/C.

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Received 17 May 1976