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Control of time of parturition in pigs

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Summary. Injection of prostaglandin (PG) F-2α or its analogues has provided a technique to induce parturition after Day 110 of gestation in the sow. The mean interval from PG injection to parturition ranges from 24 to 28 h, but only 50–60% of the sows farrow during an 8–10 h working day, and as many as 20% of sows may begin parturition before the injection of PG or < 22 h after the injection. The duration of parturition is positively associated with the incidence of stillbirths and perinatal death so that techniques to reduce the duration of parturition may save piglets. Early parturition has been prevented by feeding sows progestagens, PG synthesis inhibitors and hypothalamic function inhibitors. These compounds were detrimental to piglet survival if they delayed parturition too long after the expected time of parturition. Parturition was delayed in sows up to 1·5 days by altrenogest, 1·6 days by meclofenamic acid, 2·7 days by indomethacin, and 3 days by methallibure without increased incidence of stillborn piglets compared with control sows. Injection of PG after administration of altrenogest or meclofenamic acid was successful in experiments with sows; parturition could be confined to a 5-day working week with no increase in stillborn piglets compared with control sows. Relaxin injected at 48 and 24 h before or only 24 h before injection of PG increased the proportion of sows farrowing 22–32 h after PG to 86·2% compared with sows injected only with PG (53·3%, $P < 0·01$). Oxytocin injected 20 h after injection of PG increased the proportion of sows farrowing 20–28 h after PG to 90·4% compared with sows injected only with PG (49·2%, $P < 0·005$). Injection of 25–60 i.u. ACTH on Day 110 of gestation did not shorten the length of gestation, but did decrease the incidence of stillborn piglets by 0·2 piglets/litter ($P < 0·05$). An injection of the β-adrenergic antagonist, carazolol, during labour before the birth of the first piglet decreased the duration of parturition and the incidence of stillborn piglets particularly in primiparous sows ($P < 0·05$). Carazolol injected with oxytocin 20 h after injection of PG decreased the interval from PG to parturition by 2 h compared with sows injected with only PG and oxytocin. These results indicate that the use of early parturition blockers such as altrenogest or meclofenamic acid with PG and agents such as oxytocin, relaxin or carazolol should be investigated to enhance further control of timing of parturition in the sow and to decrease perinatal piglet mortality.

Why more precise control of parturition?

More precise control over timing of parturition of sows becomes increasingly important as producers seek to increase litter size and to maximize postnatal piglet survival. Studies on postnatal piglet survival reviewed by Leman, Hurtgen & Hilley (1979) indicated that 20–25% of piglets died before weaning and that most of this loss occurred during the first 3 days of the piglet's life. The incidence of stillbirths and perinatal deaths increased as litter size increased and as the duration of parturition increased. Randall (1972) concluded that piglet survival at birth was most influenced by fetal hypoxia. Temporary hypoxia during birth may cause permanent damage as piglets dying

before 21 days *post partum* had higher blood lactate at birth than piglets that survived (English & Smith, 1975).

Even if the occurrence of stillborn piglets cannot be eliminated, the presence of an attendant during parturition to assist difficult deliveries manually (Hammond & Matty, 1980) and to resuscitate piglets (Milosavljevic *et al.*, 1972) may save up to one additional piglet per litter. In addition, other potential benefits derived from the ability to induce parturition more precisely are (1) more efficient use of farrowing facilities, (2) parturition during regular working hours, (3) efficient cross-fostering of litters, (4) better synchronization of oestrus in sows after weaning, and (5) more uniform age and weight of piglets in their feeding quarters.

Use of prostaglandin F-2α analogues

The most effective method for induction of parturition in sows has been an intramuscular injection of PGF-2α or one of its analogues. First, Lohse & Nara (1982) reviewed the literature on the use of this method in sows on or after Day 110 of gestation. Induction of parturition did not appear to differ among PGF-2α analogues except for the magnitude of the effective dose. However, some of the PGF-2α compounds do differ with respect to effects on behaviour and respiration and on uterine contractile activity (Taverne, 1982; Bonte, Coryn, Moyaert & Vandeplassche, 1984). Sows began to farrow an average of 24–28 h after injection of PGF-2α or an analogue. Over 90% of the sows began farrowing within 48 h after injection (First *et al.*, 1982), but typically only 50–60% began farrowing during an 8–10 h interval on the expected day of parturition. In experiments in which induction of parturition was compared with non-induction, no consistent differences have been found in litter size, % piglets stillborn, number of piglets weaned/litter or litter weight at weaning.

This paper will review techniques that have been developed and in some cases combined with PGF-2α analogue treatment to control the time of parturition more precisely and to decrease the duration of parturition in sows.

Use of progestagens

Nellor (1963) first demonstrated the effectiveness of an orally active progestagen, MAP (6-methyl-17-acetoxyprogesterone), in delaying parturition in the sow. Use of MAP at dosages of 0·09 to 0·364 mg/kg body weight each day delayed early parturition and did not increase gestation length or incidence of stillborn piglets if feeding was terminated on the day of milk let down, 6–24 h before delivery of the first piglet (Nellor, Daniels, Hoefer, Wildt & Dukelow, 1975). However, if MAP feeding was continued past the day of milk let down on Day 114, to Days 115–124, birth was delayed to Days 116–129 and the incidence of stillborn piglets was high. When gestation was prolonged for more than 4 days after milk let down, mammary glands involuted and milk could not be manually expressed (Nellor *et al.*, 1975). Delay of parturition and high levels of MAP (up to 0·875 mg/kg body weight twice daily) had no detectable detrimental effect on survival of piglets *in utero* (Nellor, 1963; Curtis, Rogler & Martin, 1969; Nellor *et al.*, 1975); live piglets were delivered by Caesarean section up to 6 days after the expected day of parturition. Piglet birth weights, survival, and growth for 7 days *post partum* did not differ among piglets recovered by Caesarean section on Day 119 compared with natural birth on Day 113 of gestation (Curtis *et al.*, 1969). Another orally active progestagen, CAP (6α-6-dehydroacetatoxyprogesterone), has been administered orally to sows from Day 108 to parturition at dosages of 30–50 mg/day without lengthening gestation (Jochle, Orozco, Zerobin, Esparza & Hidalgo, 1974). However, incidence of stillborn piglets was increased from 2·5% in control sows to 10·4% and 28·2% in sows fed 30 and 50 mg CAP daily. Dystocia after progestagen treatment has been associated with a decrease in uterine

electrical activity and contractions associated with stage II of labour (delivery of piglets) in sows observed by Nellor *et al.* (1975) and Jochle *et al.* (1974).

Injections of progesterone have effects on gestating sows similar to those of oral progestagens. Daily injections of 500 mg progesterone from Day 110 to Day 120 of gestation delayed parturition (First & Staigmiller, 1973). In this study about half the piglets were alive in the uterus at 120 days, but the number alive in the uterus decreased to less than 1 piglet/litter at 130 days. Successful parturition after termination of progesterone treatment required that progesterone withdrawal be synchronized with luteolysis and relaxin secretion. Very high doses of progesterone (500 mg/day) terminated on Day 114 delayed parturition to Day 117·5 compared with Day 115 in control sows, and the incidence of stillborn piglets was 52% (Coggins, Van Horn & First, 1977). A delay of parturition by 2·3 days beyond that of control sows increased the duration of parturition and the incidence of stillborn piglets to 50% or more (Sherwood, Wilson, Edgerton & Chang, 1978; Taverne *et al.*, 1982). Plasma progesterone on the day before parturition was higher in sows experiencing dystocia, with mean of 7·6 ng/ml for sows farrowing on Day 116 and 9·0 ng/ml for sows farrowing on Day 118 compared with 2·9 ng/ml for control sows farrowing on Day 114 (Wilson, Edgerton, Cromwell & Stahly, 1981).

Progesterone treatment of sows past the expected time of parturition did not interfere with luteolysis, milk let down and prepartum release of relaxin and prolactin (Sherwood *et al.*, 1978; Taverne *et al.*, 1982) which were detected at the same point in gestation in treated as in control sows. However, some disagreement was found with respect to plasma oestrogen concentrations. When oestradiol-17β was specifically measured in 3 sows injected with progesterone, no decrease in plasma oestradiol-17β was detected until parturition on Days 117–118 (Taverne *et al.*, 1982). In contrast, while plasma unconjugated oestrogen had not decreased to post-partum levels, it was markedly lower during the 48-h interval before parturition on Day 118 in 4 progesterone-treated sows than in 4 control sows farrowing on Day 113·8 (Wilson *et al.*, 1981).

Most circulating oestrogen in sows during gestation is of intrauterine origin, but the role of oestrogen in the events of parturition has not been elucidated for the sow. Expression of oestrogen action is dependent on progesterone withdrawal for prepartum cellular changes such as formation of gap junctions between cells in the myometrium, oxytocin receptors in the myometrium and relaxin receptors in the myometrium and cervix (Liggins, 1979; Garfield, Puri & Csapo, 1982; Mercado-Simmen, Goodwin, Ueno, Yamamoto & Bryant-Greenwood, 1982; Fuchs, Periyasamy, Alexandrova & Soloff, 1983; Downing & Sherwood, 1985). Therefore, oestrogen treatment following progesterone withdrawal in the sow might promote prepartum cellular changes in the reproductive tract to improve chances of successful parturition. The incidence of stillborn piglets was decreased in an experiment by Wilson *et al.* (1979) who administered no injection, 3 mg oestradiol benzoate or 10 mg PGF-2α to sows 6 h after the last injections of progesterone on Day 113 of gestation. The injection of oestradiol benzoate resulted in 100% of piglets being born alive compared with 50% for sows injected with PGF-2α and 66·8% for sows not injected.

Besides preparing the sow for parturition, oestrogen may also adapt piglets for postnatal life. Hacker *et al.* (1979) reported that urinary oestrone increased to a greater extent during the last 4 days of gestation in 3 of 6 sows studied. The 3 sows with more urinary oestrone had no stillborn piglets and somewhat heavier piglets at birth which were more active and quicker to suck than piglets from the other 3 sows which had 10·3% of their piglets stillborn. Based on behaviour after injection of oestradiol benzoate into piglets at birth, Bate & Hacker (1982) proposed that oestradiol or a metabolite was utilized in the central nervous system of the piglets to promote activity and decrease the time from birth to suckling.

Injection of sows with oestradiol benzoate has been included in other techniques to control time of parturition in sows without beneficial effect and will be referred to later.

Gooneratne, Hartmann, McCauley & Martin (1979) used a combination of progesterone and a PGF-2α analogue, cloprostenol, to control successfully time of parturition in sows. Three groups of 25 sows were assigned to the following treatments: (1) control, 5 injections of peanut oil vehicle at

10:00 h on Day 112 and at 10:00 and 20:00 h on Day 113 and 114; (2) 5 injections of progesterone, 100 mg on Day 112 and 50 mg/injection on Days 113 and 114; and (3) 5 injections of progesterone followed by 200 μg cloprostenol at 10:00 h on Day 115.

As shown in Table 1, gestation length was 0·9 days longer in sows injected only with progesterone than in control sows. The time from the last progesterone injection to parturition was reduced by cloprostenol injection. The synchrony of farrowing after progesterone and cloprostenol was very good with 80% of the sows beginning parturition between 08:00 and 17:00 h on Day 116. Total litter number and weight at birth and 19 days *post partum* (Table 2) did not differ significantly among treatments. The incidence of stillborn piglets appeared to be greater in treated sows than in controls, but this was not statistically evaluated. The success of this experiment was probably due to the relatively low total dose of progesterone (300 mg) that these sows received and to the fact that progesterone injections were terminated 24 h before the mean gestation length for the population of sows under investigation. Plasma progesterone was not excessively elevated for long periods of time and averaged 1·2, 2·4 and 3·2 ng/ml at parturition in sows on treatments 1, 2 and 3, respectively.

Table 1. Effects of progesterone and cloprostenol (PG) on gestation length in sows (mean ± s.e.m.) (after Gooneratne *et al.*, 1979)

Treatment	No. of sows	Day of parturition	Hours after last injection	
			Progesterone	PG
1 Control	25	115·5 ± 0·2[b]		
2 Progesterone	25	116·4 ± 0·4[c]	48·5 ± 3[b]	
3 Progesterone + PG	25	116·0 ± 0·1[c]	36·6 ± 1[c]	25·4 ± 1

[bc] Means within a column with no superscript letter in common differ $P < 0·05$ (Student's t test).

Table 2. Piglet survival at birth and at 19 days *post partum* after treatment of sows with progesterone and cloprostenol (PG) to control time of parturition (after Gooneratne *et al.*, 1979)

Treatment	Live piglets/litter	% piglets stillborn	% survival of piglets born alive to Day 19	Litter weight at 19 days (kg)
1 Control	9·4 ± 0·5	3·3	95·3	35·2 ± 2·2
2 Progesterone	9·3 ± 0·5	12·8	95·9	37·8 ± 1·4
3 Progesterone + PG	9·2 ± 0·5	9·8	90·0	36·9 ± 1·3

Values are mean ± s.e.m.

Altrenogest (17α-allyl-oestratriene-4,9,11,17α-ol-3-one) has been used to control the time of parturition in sows (Varley & Brooking, 1981; Ledward, English, Davison, Smith & Varley, 1982; Guthrie, Meckley & Pursel, 1984). As with MAP (Nellor *et al.*, 1975) and progesterone (First & Staigmiller, 1973; Coggins *et al.*, 1977; Sherwood *et al.*, 1978), lengthening gestation to 120 or 122 days by feeding altrenogest to Day 118 or 120 increased the incidence of stillborn piglets to 25% (compared with 1·4% in controls; Varley & Brooking, 1981). In the same study, injection of 5 mg oestradiol benzoate 6 h after last feeding of altrenogest on Day 116 did not decrease the incidence of stillborn piglets (20·4%, compared with 3·9% in untreated control sows). Termination of altrenogest treatment on the expected day of parturition, Day 115, increased the incidence of stillborn piglets to 14·3% and the length of gestation to 116·8 days (compared with 3% stillborn piglets and a 115·1 day gestation in untreated control sows; Ledward *et al.*, 1982).

An experiment using altrenogest and a PGF-2α analogue (Lutalyse) was conducted at the University of Delaware Swine Research Station at Georgetown, Delaware (Guthrie *et al.*, 1984). The experimental design is given in Table 3. Four treatments were administered: (1) control, no treatment, (2) 15 mg PGF-2α at 10:00 h on Day 111 or 112, (3) a total of 20 mg altrenogest/day fed twice daily on Days 109–112 or 110–113, and (4) altrenogest as fed in Treatment 3 followed by 15 mg PGF-2α at 10:00 h on the day after the last feeding of altrenogest. Altogether, 82 primiparous and multiparous sows were used for 127 farrowings.

Table 3. Treatment protocols using altrenogest (AT) and PGF-2α for control of parturition in the pig

Group	Treatment	Expected day of parturition
1	1 Control (no treatment)	114
	2 PGF-2α (15 mg) 10:00 h on Day 111	112
	3 AT (20 mg) Days 109–112	114
	4 AT Days 109–112; PGF-2α 10:00 h on Day 113	114
2	1 Control	114
	2 PGF-2α 10:00 h on Day 112	113
	3 AT Days 110–113	115
	4 AT Days 110–113; PGF-2α 10:00 h on Day 114	115

Day 0, first day of oestrus, was designated as Day 0 of gestation.

Table 4. Effects of altrenogest and PG (Lutalyse) on gestation length in sows (mean ± s.e.m.)

Treatment	No. of litters	Day of parturition	Hours to parturition*	Hours after last injection	
				Altrenogest	PG
1 Control	35	113·5 ± 0·4[a]	39·7 ± 9·1[a]		
2 PG	31	112·7 ± 0·1[b]	18·2 ± 3·0[b]		25·3 ± 3·5[a]
3 Altrenogest	30	115·2 ± 0·2[c]	78·1 ± 4·5[c]	61·5 ± 4·7[a]	
4 Altrenogest + PG	31	114·4 ± 0·1[d]	59·7 ± 2·6[d]	40·5 ± 1·4[b]	24·6 ± 1·4[a]

[abcd] Means within a column with no superscript in common differ by Duncan's Multiple Range Test ($P < 0·05$).
* From 10:00 h on Day 112.

The day of gestation when treatment with PGF-2α and/or altrenogest was started and ended had no significant effect on gestation length or piglet birth data, so means for Groups 1 and 2 were combined (Table 4). The single injection of PGF-2α on Day 111 or 112 shortened gestation by an average of 21 h ($P < 0·05$), while treatment with altrenogest lengthened gestation by 38·4 h ($P < 0·05$) compared with control sows with a 113·5-day gestation. Sows began to farrow about 25 h after the injection of PGF-2α (Treatments 2 and 4). Injection of PGF-2α hastened the onset of parturition after feeding altrenogest by 21 h ($P < 0·05$) compared with sows fed altrenogest and not injected. Use of PGF-2α alone or after altrenogest feeding improved the precision of parturition. Only 5 of 35 control sows began farrowing between 06:00 and 18:00 h on Day 114, the expected day of parturition, compared with 43 of 62 sows which began farrowing 18–30 h after the injection of PGF-2α (Treatments 2 and 4). Seven of 30 sows in Treatment 3 began farrowing between 06:00 and 18:00 h on Day 114 or 115. No sows began parturition before the last feeding of altrenogest.

The duration of parturition and litter survival and weight at birth and at weaning at 21 days *post partum* did not differ among treatment groups and the means from all four treatment groups are combined in Table 5.

Table 5. Litter parameters at birth and 21 days *post partum* combined for control sows and sows treated with PGF-2α and/or altrenogest

	No. of litters	Mean ± s.e.m.
Duration of parturition (h)	122	4·6 ± 0·3
Live piglets/litter	127	9·6 ± 0·3
% piglets born alive	127	90·0 ± 1·3
Live litter weight (kg)	126	13·7 ± 0·4
% piglets weaned/total born alive	126	80·4 ± 2·0
Live litter weight 21 days (kg)	121	48·0 ± 1·4

Table 6. Effect of 200 mg methallibure fed daily from Day 110 to term on parturition in sows (mean ± s.d.) (after First, 1972)

Treatment	No. of sows	Day of milk let down	Gestation length (days)	Piglets born/ litter	% piglets stillborn	Live weight/ piglet (kg)
Control	7	114·1 ± 2·0	114·1 ± 2·0	6·9	2·2	1·39
Methallibure	7	118·0 ± 2·4*	118·0 ± 2·4*	9·7	4·2	1·43

* Mean greater than that of control ($P < 0·05$).

Use of inhibitors of hypothalamic function

The fetal brain provides one or more signals which initiate events leading to parturition (First & Bosc, 1979). One signal may be expressed through the 10-fold increase in secretion of cortisol by the fetus during the last 10 days of gestation. Methallibure (a compound inhibiting hypothalamic regulation of the anterior and posterior pituitary) was fed at a dose of 150–200 mg daily from Day 100 of gestation to term. Methallibure delayed parturition but could not prevent it from occurring on Days 117–118 (First, 1972; Coggins & First, 1977). Methallibure also delayed dexamethasone-induced parturition, suggesting another site of action besides the anterior pituitary–adrenal cortex axis of the fetuses. Luteolysis (Coggins & First, 1977) and milk let down (First, 1972) were not detected at the expected time of parturition (Day 114), but were delayed until just before the actual day of parturition. The weight of piglets at birth and incidence of stillborn piglets were not different between parturition on Day 114 and Day 118 (Table 6). However, by 7 days *post partum* an average of 2·7 piglets/litter had died in litters from sows fed methallibure compared with none in litters from control sows; the mean piglet weight at this time was 2·50 kg from control sows and 2·31 kg from methallibure-fed sows. Long-term feeding of methallibure may have interfered with lactation; methallibure is known to block oxytocin release (Garbers & First, 1968). These results indicate that compounds such as methallibure used in a treatment protocol similar to that for progesterone (Gooneratne *et al.*, 1979) or altrenogest (Guthrie *et al.*, 1984) might be highly efficient in controlling time of parturition in sows. However, little is known about the effects of methallibure or similar compounds on the final stages of organ maturation in fetuses.

Use of inhibitors of prostaglandin synthesis

PGF-2α has been implicated as the agent responsible for luteolysis in the sow as indomethacin administration delayed luteolysis, delayed increased plasma 13,14-dihydro-15-keto-PGF-2α (PFGM) and delayed parturition until treatment was terminated (Nara & First, 1981b; Taverne *et al.*, 1982).

Additional experiments using indomethacin have shown that prostaglandin production after PGF-2α induced luteolysis is essential for successful parturition in the sow (Nara & First, 1981a, b). A PGF-2α infusion for 10 h (5 mg total) on Day 110 of gestation was sufficient to induce luteolysis, and parturition started about 30 h after the beginning of infusion. In contrast, when PGF-2α was infused in sows being injected with indomethacin, luteolysis was induced, but parturition was delayed to 66 h after the start of infusion and 74% of piglets were stillborn. Only when more PGF-2α was infused, up to a dose of 66 mg over a 33-h period, could the inhibitory effects of indomethacin treatment be overcome, with parturition starting 30 h after beginning the infusion and only 10·1% of piglets being stillborn.

Gooneratne, Hartmann & Barker (1982) have investigated the practical application of the prostaglandin synthesis inhibitor, meclofenamic acid (MFA), to parturition control in sows. Meclofenamic acid was fed twice daily at a total daily dose of 5 mg/kg body weight/sow/day on Days 112–114 to two groups of sows; one group was injected with 200 μg cloprostenol on Day 115 and the other was not. Parturition was delayed by about 1·6 days by treatment with MFA compared with untreated controls (Table 7). Injection of cloprostenol did not change the time between last feeding of MFA and parturition, but cloprostenol reduced the variation in time from last MFA to parturition (range of 17–52 h with cloprostenol compared to 15–75 h with MFA alone). A few sows fed MFA in treatment Group 2 (Table 7) had prolonged parturition, but no manual assistance for these sows was required. The incidence of stillborn piglets, which was < 10%, litter weight and piglet survival to weaning did not differ amongst the treatment groups. No problems in piglet development after the feeding of MFA were reported (Gooneratne *et al.*, 1982), and no significant differences in piglet survival or litter weight among treatment groups at weaning were detected.

Table 7. Effect of meclofenamic acid (MFA) and 200 μg cloprostenol on parturition in sows (mean ± s.e.m.) (after Gooneratne *et al.*, 1982)

Treatment	No. of litters	Day of parturition	Live piglets/ litter	% piglets stillborn	Weaning at 19 days *post partum*	
					Litter size	Litter weight (kg)
1 Control	16	114·4 ± 0·2[b]	10·1 ± 0·4	5·1	8·9	35·5
2 MFA	16	116·0 ± 0·2[c]	10·4 ± 0·6	7·9	9·0	35·1
3 MFA + cloprostenol	32	116·0 ± 0·09[c]	10·1 ± 0·6	9·1	8·7	34·8

[bc] Means within a column with no superscript letter in common differ by Student's *t* test ($P < 0·05$).

Parturition of sows can be delayed longer with PG synthesis inhibitors than with progesterone without adverse effects. Indomethacin administered orally from Days 110 to 115 of gestation delayed parturition to Day 117·7 (2·7 days longer than in control sows) without increasing the incidence of stillborn piglets (Taverne *et al.*, 1982). However, injections of indomethacin from Day 109 to Day 116 delayed parturition to Day 120 and 58·3% of the piglets were stillborn (Nara & First, 1981b). Unlike progestagen treatment, treatment with indomethacin kept endocrine profiles (PGFM, progesterone, relaxin, prolactin and oestradiol-17β) in their proper sequence. However, the sequence shifted from the time of parturition in control sows to the new time of parturition determined by withdrawal of indomethacin (Sherwood, Nara, Crnekovic & First, 1979; Nara & First, 1981b; Taverne *et al.*, 1982). The high incidence of stillborn piglets in sows starting parturition at 120 days (58·3%) did not appear to be due to the lack of expression of endocrine signals, but may have been due to failure of the reproductive tract or the feto-placental complex to respond at the cellular level.

Use of relaxin

Ablation of corpora lutea and relaxin replacement have shown that relaxin secretion by corpora lutea is essential for successful natural parturition in the sow (Nara, Welk, Rutherford, Sherwood & First, 1982). Butler & Boyd (1983) investigated the use of pig relaxin to reduce the variability in time between an injection of PGF-2α and parturition in sows. Sows were assigned to four treatment groups; sows in Group 1 were injected with saline and sows in Groups 2–4 were injected with 10 mg PGF-2α (Lutalyse) at 08:00 h on Day 112 of gestation. Sows in Groups 3 and 4 were also injected with 600 i.u. pig relaxin; sows in Group 3 at 24 h, and sows in Group 4 at 24 and 48 h before injection of PGF-2α.

Injection of PGF-2α alone decreased the length of gestation ($P < 0{\cdot}01$) by about 40 h and decreased the variation compared with control sows (Table 8). Injection of relaxin before PGF-2α did not decrease the length of gestation further, but did reduce the variation of sows in Groups 3 and 4 compared with sows injected with PGF-2α alone when one sow farrowing 73·1 h after injection of PGF-2α in Group 4 was excluded from the data. The proportion of sows that began parturition 22–32 h after injection of PGF-2α was greater in sows injected with relaxin (86·2%) than in sows injected only with PGF-2α (53·3%) ($\chi^2 = 5{\cdot}7$, $P < 0{\cdot}01$). The incidence of stillborn piglets was < 10%. Piglet survival and growth to weaning at 21 days *post partum* did not differ among treatment groups.

Table 8. Effect of PGF-2α and relaxin on parturition in sows (after Butler & Boyd, 1983)

Treatment	No. of sows: Treated	No. of sows: Farrowing 22–32 h after PG (%)	Hours from Day 112 to parturition	% piglets stillborn
1 Saline	15		$69{\cdot}6^{b} \pm 30{\cdot}6^{b}$	1·0
2 PGF-2α, Day 112	15	8 (53·3)	$30{\cdot}4^{c} \pm 9{\cdot}4^{c}$	7·5
3 Relaxin (Day 111)+PGF-2α (Day 112)	14	12 (85·7)	$25{\cdot}9^{c} \pm 3{\cdot}7^{d}$	3·6
4 Relaxin (Days 110 & 111)+ PGF-2α (Day 112)	15	13 (86·7)	$27{\cdot}0^{c} \pm 2{\cdot}9^{d}$	1·2

[bcd] Means and s.d. within a column with no superscript letter in common differ ($P < 0{\cdot}01$).

Use of corticoids or ACTH

The use of glucocorticoids would appear to have little practical use for induction of parturition in the sow. North, Hauser & First (1973) and Coggins *et al.* (1977) reported successful induction of parturition with the synthetic corticoid, dexamethasone, injected for 4 days at doses of 75 or 100 mg/day. These doses exceed those recommended for therapeutic use (Carroll, 1974), and doses in the therapeutic range, 10–20 mg, failed to induce parturition (Rich, Libal, Dunn & Wahlstrom, 1972). Another possible disadvantage of corticoid-induced parturition could be reduction in live birth weight of piglets born of sows injected with dexamethasone (North *et al.*, 1973).

ACTH has induced parturition successfully only after injection into the fetus (First *et al.*, 1982). However, 25–60 i.u. ACTH injected intramuscularly into sows on Day 110 of gestation reduced the duration of parturition significantly (Ludvigsen, 1982) and reduced the incidence of stillborn piglets by 40–50% in 103 sows (Ludvigsen, 1982) and in 442 sows (Johnston, Stelmasiak, Thornton & Evans, 1984), compared with similar numbers of untreated sows. This technique was calculated to provide 0·2 more piglets born alive/litter (Johnston *et al.*, 1984). ACTH would be expected to increase plasma corticoids in the sow and may have increased the amount of corticoid reaching the

fetal lungs and small intestine. Exposure of fetuses to various corticoids caused precocious maturation of these organs under experimental conditions (Olson, 1979). A small advance in prenatal organ maturation could enhance postnatal survival and may contribute to induction of parturition as suggested by Olson (1979).

Use of oxytocin

Oxytocin is commonly used as an aid to parturition for sows diagnosed as suffering from uterine inertia. However, Bonte *et al.* (1984) reported that uterine inertia (lack of contractile activity) was rare during intervals of prolonged delivery. Normal patterns of myometrial electrical activity were found even when delivery was interrupted for more than an hour. Intramuscular injection of more than 10 i.u. oxytocin during delayed delivery replaced the delivery pattern of contractions with uterine tetany for 10–15 min. Bonte *et al.* (1984) suggested that this massive contractile effort could disrupt blood flow to the placenta, putting the fetuses at risk of hypoxia.

Oxytocin may not be an essential part of natural parturition (Liggins, 1979; Burden, Gorewit, Louis, Muse & Lawrence, 1982). In rats, lesions in the median eminence, which impair milk secretion and ejection and ablation of the neurohypophysis, did not block parturition. In the pig (Forsling *et al.*, 1979) and other species (Liggins, 1979), increased secretion of oxytocin is probably a result of the presence of piglets in the birth canal rather than a signal to start parturition. Oxytocin does influence smooth muscle contractile activity by lowering the threshold potential for initiation of action potentials in myometrial cells and by increasing influx of calcium (Liggins, 1979). Oxytocin also induced the release of PGF-2α in pigs (Gall, 1983) and other species (Liggins, 1979) which could assist in maintaining myometrial contractile activity during parturition.

Experimentally, the effect of oxytocin on parturition has been tested by injection after milk let down, after onset of parturition, and when the interval between piglets was >1 h (Muhrer, Shippen & Lasley, 1955; Pejsak & Tereszczuk, 1982). The results of these studies indicated that oxytocin hastened the delivery of the first piglet and shortened the duration of parturition compared with untreated sows. Used in this way, oxytocin was not found to exert any adverse effects on sows or piglets, and the incidence of stillborn piglets tended to be reduced (Pejsak & Tereszczuk, 1982). Welk & First (1980) injected oxytocin into cloprostenol-treated sows 2 h after milk let down or 28 h after PG injection, whichever came first, and reduced the time to delivery.

Recently, studies have been undertaken to control the time of parturition more precisely (i.e. to reduce variation or range in parturition time) by injecting oxytocin after an injection of PG. Oxytocin has been injected at a fixed time 22–28 h after injection of PG, shortly before the expected time of induced parturition (Exps 1–4, Table 9). In Exps 1 and 3, only 60% of the sows began parturition during working hours, defined as the 10-h interval 23–33 h after PG injection. Data from Exps 3 and 4 indicated that the number of sows farrowing during working hours was not increased by oxytocin injected so closely to the time of expected natural parturition.

Sows in one group in Exp. 2 (Table 9) were injected with 5 mg oestradiol benzoate 6 h after injection of PG. When sows farrowing only during working hours were considered, oestradiol benzoate did not decrease the mean or variation in the time from PG to first piglet.

Data from Holtz, Hartman & Welp (1983) and Welp, Jochle & Holtz (1984) (Exps 2 and 3, Table 10) indicated that oxytocin injected 20 h after PG increased the number of sows beginning parturition during working hours. In Exps 2 and 3 combined, 31 of 63 (49·2%) of PG-treated sows began parturition during working hours, defined as 20–28 h after PG, compared with 150 of 166 (90·4%) of PG-treated sows injected with oxytocin ($\chi^2 = 46{\cdot}7$, $P < 0{\cdot}005$). Precision of parturition control in Exps 2 and 3, estimated by smaller standard deviations from the mean, was significantly greater in sows injected with PG and oxytocin than in sows not injected with oxytocin. The disadvantage of oxytocin injection was a cessation of delivery after the first or second piglet, particularly with higher doses of oxytocin (Exp. 3). The low incidence of stillborn piglets was due to

Table 9. Effect of oxytocin on parturition induced by 10 mg PG

Exp.	Oxytocin: Dose (i.u.)	Oxytocin: Hours after PG	No. of sows: Treated	No. of sows: Farrowing during working hours (%)	Hours to parturition: After PG (mean ± s.d. or range)	Hours to parturition: After oxytocin	% piglets stillborn (mean)
1*	0		83	50 (60·2)	28·3 ± 2·2		8·0
	40	24,26,28	14	14 (100)	28·1 ± 0·9	2·2	
2*	40	24	25	20 (80)	24–25		
	40	24	28§	27 (96·4)	24–25		
3†	0		43	26 (60·5)	28·8 ± 3·7		5·1
	30	22	48	31 (64·6)	26·6 ± 4·1	4·2	4·6
4‡	20	22	101	73 (72·3)	23·9	1·9	6·0

* After Gall (1983); injections of PG on Day 111, 112 or 113; working hours defined as 23–33 h after injection of PG.
† After Blaisot & Steffan (1984); PG on Day 112 or 113; working hours defined as 22–32 h after PG.
‡ After Lens & Goovaerts (1984); PG on Day 114; working hours defined as 22–32 h after PG.
§ Sows also injected with 5 mg oestradiol benzoate 6 h after PG.

Table 10. Effect of oxytocin on parturition induced by 3·75 mg luprostiol or 2 mg alfaprostol injected on Day 112 of gestation

Exp.	Oxytocin: Dose (i.u.)	Oxytocin: Hours after PG	No. of sows: Treated	No. of sows: Farrowing during working hours (%)	Hours to parturition: After PG	Hours to parturition: After oxytocin	No. of sows requiring manual assistance	% piglets stillborn
				Luprostiol				
1*	0		20	10 (50·0)	31·8 ± 5·5			4·1
	30	24	19	11 (57·9)	26·1 ± 1·6	2·1		1·0
				Alfaprostol				
2*	0		35	20 (57·1)	25·6 ± 3·1			0·9
	30	20	28	25 (89·3)	21·7 ± 0·9	1·8		0·4
	30	24	28	22 (78·6)	25·2 ± 1·4	1·6		5·6
3†	0		28	11 (39·3)	25·7 ± 2·8		1	3·8
	5	20	32	25 (78·1)	26·1 ± 0·9	6·1	7	7·5
	10	20	33	27 (81·8)	25·2 ± 0·9	5·2	6	2·0
	20	20	34	34 (100)	22·6 ± 1·1	2·6	13	5·9
	30	20	39	39 (100)	23·1 ± 1·0	3·1	20	3·1

Values are mean ± s.d.
* After Holtz, Hartman & Welp (1983); working hours defined as first 8 h after injection of oxytocin or 20–28 h after injection of PG.
† After Welp, Jochle & Holtz (1984); working hours defined as 20–28 h after injection of PG.

prompt removal of piglets through the cervix by an attendant. The number of piglets weaned and their weaning weight and the subsequent return of sows to oestrus did not differ among treatment groups. The data of Welp *et al.* (1984) on the dose titration of oxytocin were in agreement with the conclusion of Bonte *et al.* (1984) that injections of oxytocin greater than 10 i.u. should not be used in sows.

Parturition induced by PG can range from 6 h before to 6 h after the mean for a particular population of sows. Wilson (1984) injected oxytocin 15–16 h after cloprostenol and 38 of 40 sows (95%) farrowed during working hours (approximately 08:00–16:00 h on Day 113 of gestation).

Stillbirth rate was higher (9%) when oxytocin was used than when it was not (6%). Most of the stillborn piglets were found in 5 sows with prolonged parturition. Unfortunately, in other populations of sows, prolonged parturition and stillborn piglets may often be associated with oxytocin injected several hours before the expected time of milk let down.

Control by regulation of autonomic nervous system

Compared with the large number of publications on the endocrine control of parturition in the sow (First & Bosc, 1979; First *et al.*, 1982) very little information is available on the role of the autonomic nervous system in parturition. Innervation of the uterus by the parasympathetic nervous system appears to be required for parturition in the rat (Burden *et al.*, 1982). Bilateral section of the pelvic parasympathetic nerves on Days 8–10 of gestation did not interfere with pregnancy, but parturition was blocked.

The presence of adrenergic and cholinergic nerves has been demonstrated pharmacologically in the myometrium and uterine vasculature of virtually all species (Bostedt & Rudloff, 1983). Bostedt & Rudloff (1983) proposed that the activity of the β-adrenergic receptors during late gestation in the sow reached a dominant level over the activity of α-adrenergic receptors. Other investigators have shown a biphasic response (contraction followed by relaxation for several minutes) after injection of adrenaline in sows during dioestrus, oestrus and pregnancy (Taverne, 1982). The relaxation phase of the response to adrenaline could be blocked in post-partum sows by the β-adrenergic antagonist propranolol (Ngiam, 1977). Inhibition of uterine contractions during oestrus (Bower, 1974) and during parturition (Naaktgeboren, 1979) has been reported after disturbances to the environment of the sows. The authors suggested that endogenous adrenaline acting through the β-adrenergic receptors was responsible for the inhibition. In fact, disturbance of the environment of sows on the day of expected parturition has delayed parturition and increased variation among sows in response to injection of PGF-2α analogues (Welp & Holtz, 1985).

To block untimely relaxation of the uterine myometrium during parturition or to enhance contractions, β-adrenergic antagonists have been tested in sows. A field trial utilizing 1066 sows from 204 herds was conducted by Bostedt & Rudloff (1983). Carazolol, 1-(4-carbazolyloxy)-3-α-isopropylamine-2-propanol, was injected intramuscularly at a dosage of 10 μg/kg body weight after milk let down and before the birth of the first piglet. Carazolol treatment significantly decreased the duration of parturition, the % of piglets stillborn and % of piglets manually delivered. The reduction by carazolol of the duration of parturition and the incidence of stillborn piglets was greater for primiparous than multiparous sows (Table 11). Carazolol treatment decreased the number of piglets requiring manual delivery in multiparous sows but not in primiparous sows.

Table 11. Effect of the β-adrenergic antagonist carazolol on parturition in gilts and sows (after Bostedt & Rudloff, 1983)

Treatment*	Parity	No. of animals	Litter size†	% sows with parturition >6 h	% piglets stillborn	% piglets manually delivered
Vehicle	1	176	9·2±2·9	17·5	9·7	11·2
Carazolol	1	132	9·0±2·6	9·6‡	7·2‡	10·4
Vehicle	>1	367	11·5±3·0	13·2	7·7	6·4
Carazolol	>1	391	11·4±2·9	11·4	7·1	4·9‡

* Carazolol injected i.m. at a dosage of 10 μg/kg body wt after milk let down but before birth of first piglet.
† Mean ± s.e.m.
‡ Less than mean of vehicle treatment in same parity group, $P<0·05$ (χ^2).

Holtz & Welp (1984) have continued their efforts to reduce variation in response to PG by testing carazolol and oestradiol benzoate in combination with oxytocin. All sows were injected with 2 mg alfaprostol on Day 112 followed by 5 i.u. oxytocin 20 h later. Oestradiol benzoate and/or carazolol were injected immediately after oxytocin (Table 12). Of 60 sows, 52 (86·7%) farrowed during the 8-h interval after injection of oxytocin. Carazolol decreased the interval between alfaprostol injection and parturition by about 2 h and decreased the variation in response among sows to PG and oxytocin alone. Oestradiol benzoate following oxytocin alone or in combination with carazolol had no significant effect on parturition. The duration of parturition did not differ among treatment groups and none of the piglets required manual delivery.

Table 12. Effect of β-adrenergic antagonist, carazolol, and oestradiol benzoate on alfaprostol (PG) and oxytocin-induced parturition in the sow (after Holtz & Welp, 1984)

Treatment*	No. of sows		Hours to parturition		Duration of parturition‡ (h)
	Treated	Farrowing during working hours (%)†	After PG‡	After oxytocin	
Vehicle	14	12 (85·7)	23·3 ± 2·6	3·3	4·7 ± 0·8
Oestradiol benzoate	17	13 (76·5)	23·4 ± 2·8	3·4	5·9 ± 3·2
Carazolol	14	13 (92·9)	21·3 ± 1·3	1·3	4·3 ± 2·0
Oestradiol benzoate + carazolol	15	14 (93·3)	21·6 ± 1·2	1·6	5·4 ± 2·3

* PG, 2 mg on Day 112 of gestation followed by 5 i.u. oxytocin 20 h later in combination with vehicle, 2·5 mg oestradiol benzoate, 1·5 mg carazolol or oestradiol benzoate and carazolol.
† Working hours defined as 8-h interval after oxytocin injection.
‡ Mean ± s.d.

The potential for delayed parturition through the autonomic nervous system is also indicated by delay of parturition and cessation of myometrial contractions caused by β_2-adrenergic agonists. Zerobin & Kundig (1980) injected 150 μg clenbuterol (4-amino-α[(tert-butylamino)methyl]3,5-dichlor-benzylalcohol hydrochloride) during labour before birth of the first piglet or after the birth of 1–3 piglets. Injection of clenbuterol after milk let down but before birth of the first piglet delayed parturition for 15 h, without evidence of adverse effects on eventual delivery (Table 13). During the delay, regression in size of the mammary glands was observed and milk could not be expressed manually. Resumption of labour was accompanied by renewed appearance of milk. Labour in progress was terminated in about 8 min after injection of clenbuterol and parturition was interrupted for 2·8 h. Treatment was reported to have no adverse effects on piglet viability, delivery of the placenta or maternal behaviour. The authors suggested that hypertonic uterine contractions during parturition may occasionally be the cause of dystocia in cattle and pigs. The potential clinical value of β_2-adrenergic agonists for pigs has not been investigated.

Clenbuterol has been used to block parturition before scheduled Caesarian section on Day 114 of gestation (Nagy, 1982). When injected at a dosage of 150 μg every 6 h or 300 μg twice daily, clenbuterol failed to prevent parturition before Day 114. At a dosage of 300 μg every 6 h, clenbuterol prevented parturition before Day 114, but the incidence of stillborn piglets was 40%. When 300 μg clenbuterol were combined with one injection of 50 mg progesterone daily on Days 110–113, only 4% of treated sows farrowed by Day 114 compared to 46% of untreated sows.

The β-adrenergic agonist appears to act on the smooth muscle cell to antagonize contractile activity mediated by α-adrenergic, oxytocic or muscarinic receptors (Zerobin & Kundig, 1980; Bonte *et al.*, 1984; Taverne, 1982). However, in contrast to other studies, Bonte *et al.* (1984) reported that clenbuterol or another β-adrenergic agonist, isoxuprin, could not block parturition already started.

Table 13. Effect of a single intravenous injection of 150 μg β_2-adrenergic agonist clenbuterol on parturition of sows (after Zerobin & Kundig, 1980)

	Time of injection	
	After milk let down before first piglet	After birth of 1–3 piglets
No. of sows	5	7
Time to cessation of labour (min)	—	8·3 ± 2·2
Length of delay (h)	14·9 ± 1·6	2·8 ± 0·3
Duration of parturition resumed (h)	3·0 ± 0·4	2·1 ± 0·4
No. of piglets born alive/litter	7–12	7–14
No. of stillborn piglets/litter	0–1	0–3

Values are mean ± s.d.

Table 14. Effect of carbamylcholine or neostigmine on the incidence of stillborn piglets (after Sprecher *et al.*, 1975)

Treatment*	No. of sows	Mean no. piglets born before injection	Piglets/ litter	Stillborn/litter		
				Before treatment	After treatment	Total
Saline	17	3·88	10·06	0·23	0·65	0·88
Carbamylcholine	34	3·74	9·91	0·18	0·06†	0·23†
Neostigmine	33	3·06	10·06	0·12	0·09†	0·21†

* 5 mg carbamylcholine (acetylcholine analogue) or 2 mg neostigmine (anticholinesterase) injected after birth of third to fifth piglet.

† Less than mean for saline treatment ($P < 0·01$).

Manipulation of the parasympathetic nervous system has also been attempted. Experiments using the anticholinesterase dichlorvos, marketed as a pig wormer, were discussed by Sprecher, Leman, Dziuk, Cropper & DeDecker (1974). When 4·1–13·2 mg dichlorvos/kg body weight were fed to sows for the last 21–30 days of gestation, the birth interval between piglets was significantly decreased from 16 min (control sows) to 11 min (dichlorvos-fed sows). The incidence of stillborn piglets was significantly decreased from 6% to 3%, and birth weight of piglets was positively correlated to dose of dichlorvos fed to the sows. Dichlorvos was shown to cause prolonged contraction of smooth muscle in the gastrointestinal tract and uterus.

Studies have been conducted with an acetylcholine analogue, carbamylcholine, to determine whether a single injection during an early stage of labour would decrease the duration of parturition and the incidence of stillborn piglets. In one study, 107 sows on three farms were injected with vehicle or 2 mg carbamylcholine immediately after birth of the first piglet (Sprecher *et al.*, 1974). Carbamylcholine significantly decreased the mean interval between birth of piglets, but did not decrease the incidence of stillborn piglets. The decrease in duration of parturition was primarily due to more piglets being born within 30 min of the injection. The tendency for more stillborn piglets during birth of the last half of the litter compared with the first half was not changed by carbamylcholine.

To save more piglets in the last half of the litter, Sprecher, Leman & Carlisle (1975) injected 2 mg carbamylcholine or 5 mg neostigmine (anticholinesterase) after birth of the 3rd–5th piglet (Table 14). Carbamylcholine and neostigmine decreased the number of stillborn piglets delivered after injection to 0·06 and 0·09/litter, respectively ($P < 0·0001$) compared with 0·88 for saline-injected sows. They concluded that neostigmine was better suited to farm use because carbamylcholine caused violent gastrointestinal contractions, vomiting and salivation in sows. However,

piglet survival and growth and sow return to oestrus after weaning did not differ among treatment groups. In contrast, when Wilkinson, English, Lodge & Smith (1982) injected 104 sows with neostigmine during parturition, the birth interval between piglets and the incidence of stillborn piglets were not decreased. Similar results were obtained when neostigmine was injected during parturition induced by PGF-2α; duration of parturition and incidence of stillborn piglets were not decreased (Diehl & Leman, 1982).

Conclusions

Recent research indicates that techniques exist for the design of a management system to control precisely the time of parturition in sows. Progestagens such as altrenogest and PG-synthesis inhibitors such as meclofenamic acid can be used to block parturition before the injection of PG. Parturition at weekends can be avoided entirely. Synchronization of oestrus combined with parturition control could confine parturition in a group of sows to 2–3 days.

Injection of compounds such as relaxin, oxytocin, β-adrenergic antagonists, β_2-adrenergic agonists or anticholinesterases at a fixed time in relation to PG may decrease perinatal piglet mortality by decreasing the duration of parturition or by confining parturition to an 8-h work day.

Techniques developed to induce parturition artificially must be designed to account for prepartum endocrine and cellular changes required for a short, successful parturient effort. The key event in the initiation of parturition in the sow may be, as in the rat, the formation of gap junctions in the uterine myometrium which permit propagation of co-ordinated contractions throughout the whole uterus (Puri & Garfield, 1982). The nature of the endocrine and cellular processes involved in successful parturition require investigation so that techniques to control parturition are compatible with the physiological status of the sow.

The final signal that initiates parturition in the sow is unknown, but it may originate in the maternal central nervous system as proposed for other species (Lincoln & Porter, 1979). Research into the nature of signals emitted by the autonomic nervous system and the means by which they are processed in the reproductive tract may provide additional clues for development of better techniques to control parturition in sows.

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