16

THE ENDOCRINE CONTROL OF PARTURITION

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The pig evolved as a litter bearing species with the maintenance of pregnancy dependent on the continued presence of the litter *in utero* and on continued production of ovarian progesterone. The length of gestation is reasonably precise, being approximately 112–116 days depending on the breed, size of litter and season (Cox, 1964; Bichard *et al.*, 1976; Aumaitre, Deglaire and LeBost, 1979). Parturition occurs slightly more frequently in the late afternoon and at night (Bichard *et al.*, 1976; Boning, 1979) but no differences are seen in the frequency of day and night delivery when parturition is artificially induced (Hammond and Matty, 1980). For an individual herd a knowledge of the average length of gestation and exact breeding dates are essential for optimal piglet survival and growth when parturition is to be induced.

The entire parturition process requires 2–5 hours with piglets being delivered at approximately 12–16 minute intervals (Sprecher *et al.*, 1974; see *Table 16.1*). Piglets are delivered randomly from the two uterine horns (Dziuk and Harmon, 1969; Taverne *et al.*, 1977). They sometimes pass each other in birth order (Taverne *et al.*, 1977) and the placentas are delivered either in part after the emptying of one uterine horn or within approximately four hours after the last piglet is delivered (Jones, 1966). This is at a time when plasma levels of oxytocin are elevated (Taverne, 1979). Parturition is normally preceded by udder oedema, attempted maternal nest building and a milk ejection response (First and Bosc, 1979).

Parturition is not without complications. Body temperature increases 13±4.1 hours before delivery of the first piglet, reaches a peak of 0.6 °C–1.2 °C above the normal of 38.3±0.3 °C and in healthy sows returns to near normal within 24 hours (Elmore *et al.*, 1979). Parturition is often complicated by a disease called Mastitis–Metritis–Agalactia in which the sow's temperature remains greatly elevated for a prolonged period and she refuses to provide milk for the piglets.

Not all piglets survive farrowing; at least 6% are born dead (Randall, 1972; Sprecher *et al.*, 1974; Leman, Hurtgen and Hilley, 1979) and the last piglet in each uterine horn has less than a 50% chance of survival (Bevier and Dziuk, 1976). The factors influencing piglet survival were reviewed recently by Leman, Hurtgen and Hilley (1979). It is apparent from their

Table 16.1 A SUMMARY OF FIELD TRIALS WHERE PARTURITION HAS BEEN INDUCED IN PIGS BY PROSTAGLANDIN $F_{2\alpha}$ OR ITS ANALOGUES[a]

Prostaglandin used	*No. sows*	*Farrowing within 48 hours after treatment* (%)	*Interval treatment to first birth* (hours)	*Farrowing duration* (hours)	*Stillborn piglets* (%)	*Piglet weight*		*MMA* (%)
						birth (kg)	*weaning* (kg)	
$PGF_{2\alpha}$[b]	607	87	28±5.5	4.8±4.0	9.4	1.24±0.4	5.1±0:8	18
Control	404	12	108±39	5.1±1.2	9.4	1.33±0.2	5.7±0.7	27
Cloprostenol[c]	2473	95.3	26.4±5.7	4.2±2.8	5.3	1.30	5.6	36.7
Control	612	19	81.5±18	4.4±4.2	7.3	1.33	5.1	40.7
PGF Ay24655[d]	54	93	27.2±3		7.3	1.3		
Control	45				3.5	1.4		
Prostalene, 4 mg[e]	19	100	25.2±3.7	5.1±0.9	8.2	1.18		
5 mg	20	100	23.8±2.4	4.9±0.9		1.26		
Control	5		122±44	2.2±0.9	1.7	1.5±0.2		

[a]The data summarized are only from experiments in which $PGF_{2\alpha}$ compounds were administered at effective doses on or after day 10 of gestation.
[b]The dose of $PGF_{2\alpha}$ ranged from 7.5 to 12.5 mg i.m./sow. These data were obtained from the following publications: Ehnvall *et al.*, 1976; Backstrom *et al.*, 1976; B.N. Day, unpublished; King, Robertson and Elliott, 1979; Hagner, Elze and Michel, 1979; Hühn, Lutter and Hühn, 1980.
[c]The dose of cloprostenol ranged from 150 to 200 µg i.m./sow. The data were obtained from the following publications: Bosc and Martinat-Botte, 1976; Hammond and Carlyle, 1977; Walker, 1977; Hammond and Matty, 1980; Jainudeen and Brandenburg, 1980; Lynch and Langley, 1977; Willemse *et al.*, 1979; Pool, Copeland and Godke, 1979; Holtz, Welp and Spangenberg, 1979; Elze *et al.*, 1979.
[d]The dose of Ay24655 was 50 mg/kg/sow i.m. on day 111–113. The data are from Downey, Conlon and Baker, 1976.
[e]Prostalene was administered i.m. at doses of either 4 mg or 5 mg/sow. The data are from Holtz *et al.*, 1979.

review, and that of Dziuk (1979), that pre- and post-partum losses of piglets are sizable and may be as high as 20–25%.

Understanding the birth process and the mechanisms controlling parturition should result in ways of reducing this loss and of controlling the moment of delivery so that attendants might be present. The presence of an attendant and resuscitation of piglets has been shown to save as many as one additional piglet per litter (Milosavljevic *et al.*, 1972; Hammond and Matty, 1980). Synchronization of the moment of farrowing also results in increased efficiency of production by allowing management and handling of groups rather than individual litters.

Normal parturition in the pig requires termination of the forces maintaining pregnancy, active preparation of the foetuses for birth and of the mother for opening of the birth canal, uterine contraction, nest building and lactation. The mechanisms controlling maintenance of late pregnancy and the initiation of parturition, as well as methods for the induction of parturition in pigs, have been subjects of several recent reviews (First, 1979; First and Bosc, 1979; Dziuk, 1979; Taverne, 1979; Ellendorff *et al.*, 1979b; Silver *et al.*, 1979; Ellendorff, 1980) and will be discussed in the following sections. Evidence will be provided to show the way the foetuses initiate the birth process.

Maintenance of late pregnancy

The establishment of pregnancy and the mechanisms maintaining early pregnancy have been discussed by Bazer (Chapter 12). The maintenance of late pregnancy is graphically described in *Figure 16.1*. The reader is encouraged to consult this figure while reading the following section.

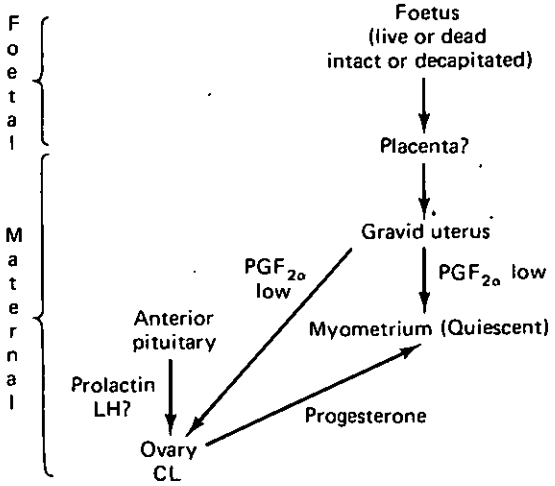

Figure 16.1 Graphic representation of the maintenance of late pregnancy in pigs. Pregnancy maintenance is dependent on a progesterone block of uterine contraction. Progesterone is from the corpora lutea. Maintenance of the corpora lutea and continued production of progesterone requires either LH or prolactin from the sow's pituitary gland and prevention by the foetuses, *in utero*, of prostaglandin $F_{2\alpha}$ secretion into the blood of the mother. If prostaglandin $F_{2\alpha}$ reached the ovaries, regression of the corpora lutea (CL) would occur.

In the pig, progesterone is the hormone responsible for preventing uterine contraction and maintaining gestation to term. When progesterone levels in peripheral plasma are maintained by the administration of progesterone, parturition at term (Curtis, Roger and Martin, 1969; Minar and Schilling, 1970; Nellor *et al.*, 1975; First and Staigmiller, 1973) and parturition induced by dexamethasone (a synthetic glucocorticoid) or prostaglandin $F_{2\alpha}$ (Coggins, Van Horn and First, 1977) are prevented. The principal factor in the maintenance of pregnancy in pigs seems to be the level of progesterone. The main source of progesterone throughout gestation is the corpora lutea, since ovariectomy (du Mesnil du Buisson and Dauzier, 1957; Ellicott and Dziuk, 1973; First and Staigmiller, 1973; Nara, Darmadja and First, 1975; 1981) or removal of corpora lutea (Nara, Darmadja and First, 1975; 1981) decrease progesterone levels and terminate pregnancy. Approximately 4–6 corpora lutea are needed for the production of sufficient progesterone to maintain pregnancy (Martin, Norton and Dziuk, 1977).

The identity and specificity of the luteotrophic hormone responsible for maintaining the corpora lutea and late pregnancy is not well established for pigs. Both prolactin and luteinizing hormone (LH) have been implicated. Hypophysectomy during late gestation terminates pregnancy in sows (du Mesnil du Buisson and Denamur, 1969; Kraeling and Davis, 1974) and prolactin, but not LH, maintains pregnancy after hypophysectomy at day 70 (du Mesnil du Buisson and Denamur, 1969). However, in intact pigs the corpora lutea remain responsive to LH stimulation until immediately before parturition, i.e. 41–17 hours before parturition (Parvizi *et al.*, 1976). During the two days preceding parturition, progesterone levels in plasma are independent of episodic increases in LH, whereas at three weeks pre-partum each episodic peak of LH is followed by an episodic peak of progesterone (Parvizi *et al.*, 1976).

Live or dead foetal tissue must be present in the uterus for maintenance of the corpora lutea of pregnancy. The amount of non-pregnant uterus present determines the requirement of a foetal contribution to luteal maintenance. At least four foetuses are required to establish and maintain early pregnancy (Polge, Rowson and Chang, 1966), whereas when one uterine horn is removed, pregnancy is maintained by two foetuses (Dhindsa and Dziuk, 1968) or by only one foetus when all the uterus except that portion occupied by the foetus is removed before the 14th day of pregnancy (du Mesnil du Buisson and Rombauts, 1963). Killing all foetuses after day 30 does not prevent maintenance of corpora lutea or lower plasma concentrations of progesterone up to day 60 (Webel, Reimers and Dziuk, 1975) or from day 100 to day 120 of gestation (Coggins and First, 1977) if the foetuses have not been resorbed.

However, removal of all foetuses at day 102 causes delivery of the placentas in less than 48 hours (Chiboka, Casida and First, 1976) and removal of 2–4 foetuses terminates the pregnancy in 42–72 hours (K.A. Martin and R.M. Liptrap, personal communication). These facts indicate that foetal tissue or a product of the intact conceptus, such as oestrogen (Bazer and Thatcher, 1977) must be present *in utero* to prevent the uterus from initiating luteolysis.

Hormonal changes associated with parturition and uterine contractability

Parturition, i.e. expulsion of the foetus or foetuses, is brought about by uterine contractions. Activation of the myometrium at parturition (*Figure 16.2*) is preceded by a multitude of hormonal changes in the blood of the mother and increased plasma cortisol in the foetuses (*Figures 16.3* and *16.4*). Parturition is preceded by increased foetal plasma cortisol (Fevre, Terqui and Bosc, 1975; Silver *et al.*, 1979) and by changes in maternal plasma that include: increased concentrations of oestrone and oestradiol

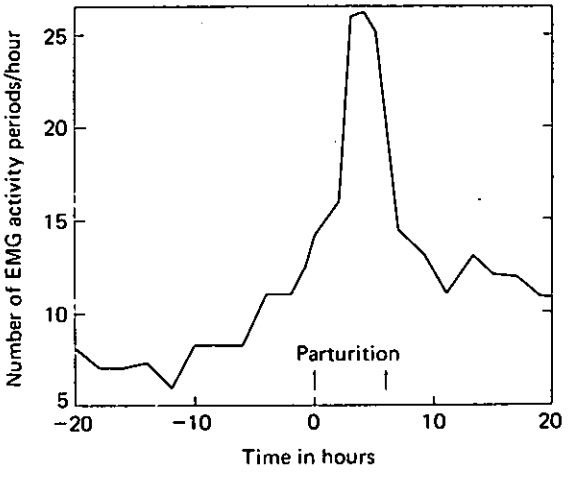

Figure 16.2 Typical changes in the frequency of uterine contractions of a sow around the time of parturition (delivery occurred at day 116). By courtesy of Dr Marie Jeanne Prud'homme, unpublished

(Ash and Heap, 1975; Fevre, Terqui and Bosc, 1975; Forsling *et al.*, 1979; Gustafsson *et al.*, 1976; Molukwu and Wagner, 1973; Robertson and King, 1974; Taverne *et al.*, 1979a,b; Wettemann *et al.*, 1977), relaxin (Sherwood *et al.*, 1975), corticosteroid (Ash and Heap, 1975; Molukwu and Wagner, 1973; Silver *et al.*, 1979), prolactin (Taverne *et al.*, 1979a; Van Landeghem and Van de Wiel, 1978), prostaglandin $F_{2\alpha}$ metabolite (Nara, 1979; Nara and First, 1977; 1981b) and oxytocin (Forsling *et al.*, 1979) at the time of delivery.

Maternal concentrations of progesterone decline within 1–2 days before parturition (Ash and Heap, 1975; Baldwin and Stabenfeldt, 1975; Coggins, Van Horn and First, 1977; Gustafsson *et al.*, 1976; Molukwu and Wagner, 1973; Nara, 1979; Nara and First, 1977; 1981b; Robertson and King, 1974; Taverne *et al.*, 1979a,b; Wettemann *et al.*, 1977; Silver *et al.*, 1979) and this rapid decline is dependent on the synthesis of prostaglandin $F_{2\alpha}$ (*Figure 16.5a*, Nara and First, 1977; 1981b). Prostaglandin $F_{2\alpha}$ increases rapidly to high concentrations during delivery (Nara, 1979; Nara and First, 1977; 1981b; Silver *et al.*, 1979) and has been shown to cause release of prolactin (Taverne *et al.*, 1979) and oxytocin in the pig (Ellendorff *et al.*, 1979a).

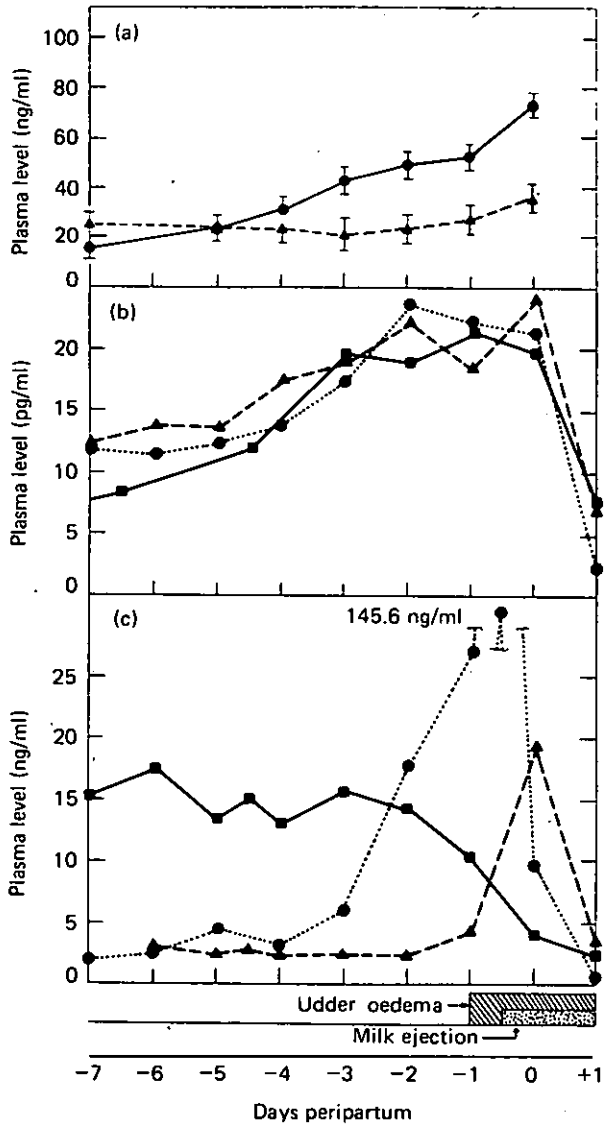

Figure 16.3 Endocrine changes preceding parturition in pigs. (a) Corticosteroids: -●-●-●- foetal cortisol, --▲--▲--▲-- maternal corticoids (Silver *et al.*, 1979); (b) -■-■-■- total oestrogens (pg × 333/ml) (Baldwin and Stabenfeldt, 1975), --▲--▲--▲-- oestradiol-17β (pg × 0.33/ml), ●...●...● oestrone (pg × 100/ml) (Molukwu and Wagner, 1973); (c) ..●...●...● relaxin (×2) (Sherwood *et al.*, 1975; 1979), -■—■—■- progesterone and --▲--▲--▲-- $PGF_{2\alpha}$ metabolite. From Nara and First (1981a,b)

Oxytocin concentrations in peripheral plasma were elevated between 9 and 4 hours before birth of the first piglet and reached their highest values during delivery of the piglets (Forsling *et al.*, 1979). The initial increase in prostaglandin $F_{2\alpha}$ concentration also causes release of relaxin (*Figures 16.5* and *16.6*; Nara, 1979; Nara and First, 1981b; Sherwood *et al.*, 1976;

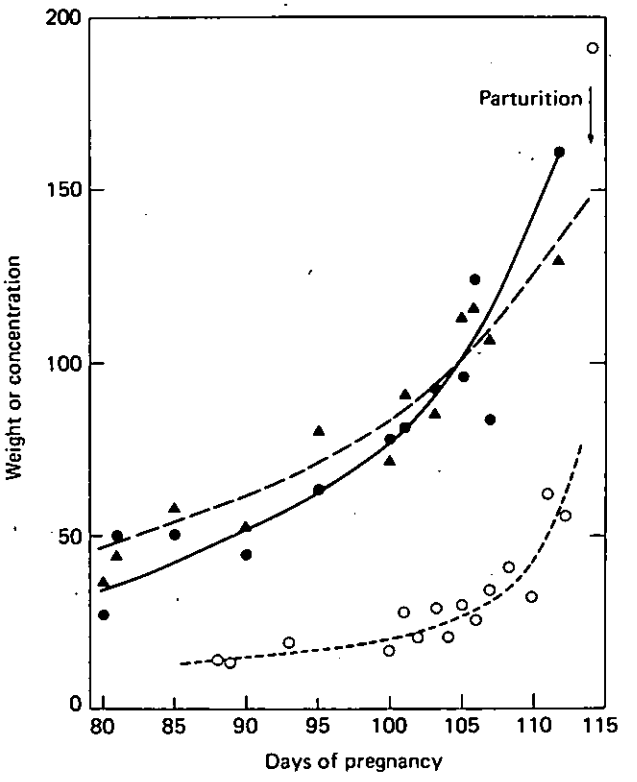

Figure 16.4 Foetal weight, ▲-- (10 g), foetal adrenal weight, ●— (mg), and foetal plasma cortisol level, O-- (ng/ml), during late pregnancy in pigs. From Bosc (1973); Fevre *et al.* (1975)

Sherwood *et al.*, 1979) and this release is prevented by inhibition of prostaglandin synthesis (Sherwood *et al.*, 1979; Nara and First, 1981b).

It has been proposed that relaxin softens or loosens the cervix (Zarrow *et al.*, 1956; Kertiles and Anderson, 1979) and thus may facilitate delivery of the foetuses. Results of a recent experiment (Nara *et al.*, 1981) show that (1) absence of relaxin in ovariectomized gilts with pregnancies maintained by exogenous progesterone causes prolonged deliveries with high incidences of stillbirths after withdrawal of the progesterone, and (2) supplementation of the progesterone treatment with highly purified porcine relaxin returns duration of delivery and frequency of live births to values similar to controls.

Udder oedema, which is indicative of milk formation, begins about 24 hours before delivery (Coggins, 1975; Coggins, Van Horn and First, 1977; Diehl *et al.*, 1974; Zerobin and Sporri, 1972) and milk ejection, an oxytocin-induced response, within 12 hours pre-partum (Nara and First, 1981a,b; see *Figure 16.3*). Exogenous oxytocin will induce labour, but only after the time that milk can be ejected (Muhrer, Shippen and Lasley, 1955).

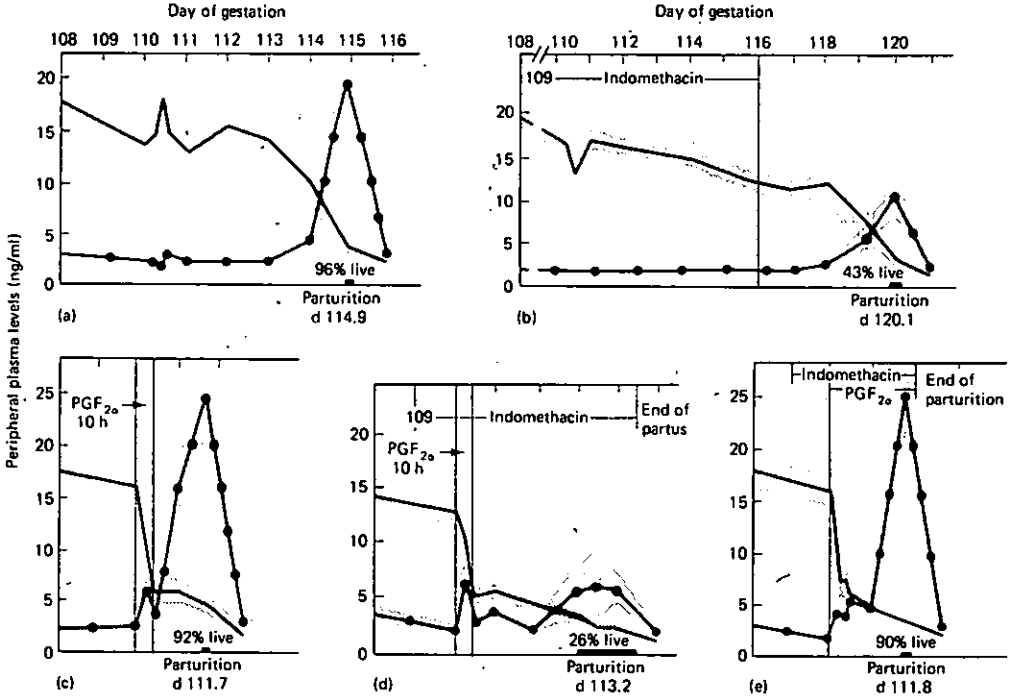

Figure 16.5 Peripheral plasma concentrations ±S.E.M. (shaded areas) of progesterone, ——, and $PGF_{2\alpha}$-metabolite ($PGF_{2\alpha}$-M) ●—●, percentage of live births (% live), duration of parturition (■) and length of gestation in sows receiving the following treatments (each, $n = 5$): (a) Control, vehicles of indomethacin and $PGF_{2\alpha}$; (b) Indomethacin (I), 4 mg I/kg 2×/day from day 109 to 116; (c) $PGF_{2\alpha}$-low (P), 0.5 P/hour infused for 10 hours on day 110; Indo + $PGF_{2\alpha}$-low (IP), treatments I and P; (d) Indo + $PGF_{2\alpha}$-low + high (IP+), treatment I + $PGF_{2\alpha}$ continuously infused from day 110 until the end of parturition starting at a rate of 0.5 mg/hour for 24 hours, followed by 3 mg/hour for 3 hours, 6 mg/hour for 3 hours and 9 mg/hour until the end of parturition. Indomethacin prevented a rise in plasma concentrations of prostaglandin $F_{2\alpha}$ metabolite and decline in progesterone. This inhibition was overcome by infusion of a luteolytic dose of $PGF_{2\alpha}$. However, normal delivery and live birth did not occur in sows receiving indomethacin until a dose of $PGF_{2\alpha}$, sufficient to cause a rise in $PGF_{2\alpha}$ metabolite comparable to that of the controls, was infused. Adapted from Nara and First (1981b).

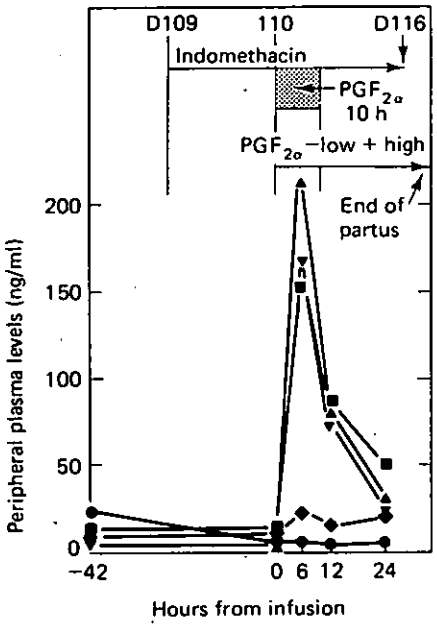

Figure 16.6 Peripheral plasma concentrations of relaxin in the sows of Figure 16.5 at –42, 0, 6, 12 and 24 hours relative to the start of infusion with $PGF_{2\alpha}$ (treatments: $PGF_{2\alpha}$-low ■, Indo + $PGF_{2\alpha}$-low ▲, and Indo + $PGF_{2\alpha}$-low + high ▼) or saline (treatments: Control ♦ and Indomethacin ●). Relaxin levels surged to peak levels ($P<0.01$) within 6 hours after infusion with $PGF_{2\alpha}$ was begun. Adapted from Nara and First (1981b)

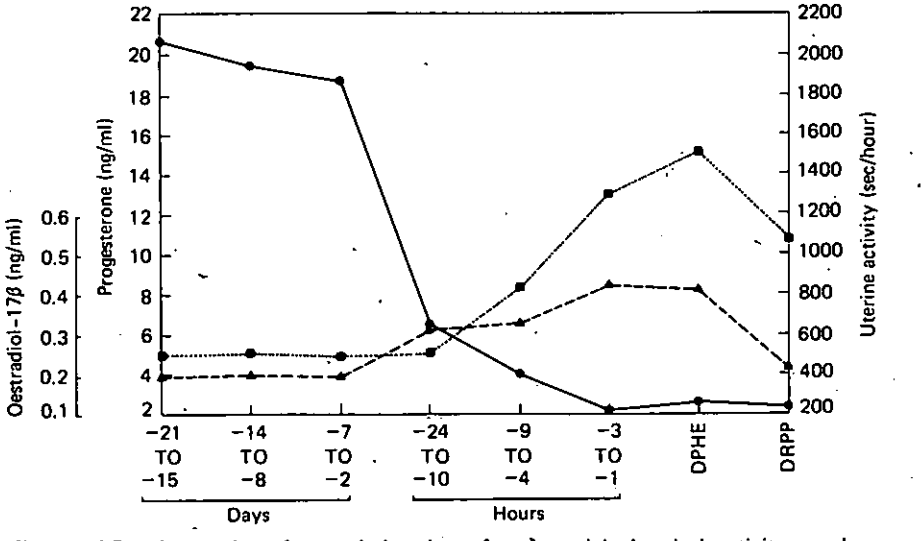

Figure 16.7 Mean values for total duration of myometrial electrical activity per hour (·■···■···■·) and plasma concentrations of progesterone (–●–●–●–), and oestradiol-17β (--▲--▲--▲--) in seven sows from 21 days before, until the end of, parturition. DPHE: hours of *D*elivery until all *P*iglets from the *H*orn with *E*lectrodes are born; DRPP: hours of *D*elivery of the *R*emaining *P*iglets and *P*lacentae. Adapted from Taverne *et al.* (1979b)

Myometrial activity during late pregnancy has been shown to consist of irregular episodes of prolonged activity in those uterine segments containing a foetus, while empty parts of the uterus remain relatively inactive (Taverne *et al.*, 1979b). At this time, plasma concentrations of oxytocin remain below 1.3 μU/ml and plasma concentrations of progesterone and oestrogen remain unchanged (Forsling *et al.*, 1979; Taverne *et al.*, 1979b). Between 24 to 10 hours before expulsion of the first piglet, when concentrations of progesterone have significantly decreased and oestrogens have increased, myometrial activity is still similar to that recorded on the previous days. Only between 9 and 4 hours before the birth of the first piglet does myometrial activity increase in all parts of the uterus (*Figure 16.7*). This increase in myometrial activity coincides with elevated concentrations of oxytocin in peripheral plasma. Uterine contractions are most frequent during delivery at the time that oxytocin concentrations are at their highest levels (Taverne *et al.*, 1979b). Release of oxytocin seems to be related to decreased concentrations of progesterone and not to increased levels of oestrogens, since oestrogen levels are already declining when oxytocin reaches its highest levels during delivery (Forsling *et al.*, 1979).

An increase in myometrial sensitivity to oxytocin near parturition has been shown to exist in rats and guinea pigs and the increased sensitivity corresponds with increased concentrations of myometrial oxytocin receptors in rats (Soloff, Alexandrova and Fernstrom, 1979) and guinea pigs (Alexandrova and Soloff, 1980c). The increase in myometrial oxytocin receptors in rats and guinea pigs appears to be correlated with a decrease in the ratio of progesterone to oestradiol concentration (P/E ratio) in the blood (Soloff, Alexandrova and Fernstrom, 1979; Alexandrova and Soloff, 1980a,b). In rats, a species requiring a decline in progesterone for the initiation of parturition, the decrease in the P/E ratio is primarily due to a decline in progesterone before spontaneous (Soloff, Alexandrova and Fernstrom, 1979; Alexandrova and Soloff, 1980a) or $PGF_{2\alpha}$-induced deliveries (Alexandrova and Soloff, 1980b). In guinea pigs, a species not experiencing a decrease in progesterone before parturition, the decrease in the P/E ratio is primarily caused by an increase in oestrogens near term (Alexandrova and Soloff, 1980b). Soloff and Swartz (1974) demonstrated the presence of oxytocin receptors in the porcine myometrium at one week before expected term. Like rats, pigs require a decrease in progesterone before parturition can be initiated and like rats, the increase in concentration of oxytocin receptors in the myometrium may be dependent on a decrease in progesterone. Lack of oxytocin receptors in the myometrium before the decline of progesterone in the blood may be the reason that oxytocin is effective in inducing deliveries in the pig only after milk can be ejected from the teats and within 24 hours before expected parturition (Muhrer, Shippen and Lasley, 1975; Welk and First, 1979; see section on *Induction of Parturition* beginning on p.330).

Maternal plasma concentrations of $PGF_{2\alpha}$ metabolite (13,14-dihydro-15-keto-$PGF_{2\alpha}$) were shown to be elevated 10–20-fold once labour had started and uterine contractions could be detected by allantoic fluid pressure changes (Silver *et al.*, 1979). It has been shown (Nara, 1979; Nara and First, 1977; 1981b) that high levels of $PGF_{2\alpha}$ are needed at parturition for

normal rapid delivery of live piglets. When $PGF_{2\alpha}$ synthesis is inhibited by adminstration of indomethacin to sows during parturition, delivery is prolonged and most of the piglets are stillborn. Infusion of high doses of $PGF_{2\alpha}$ during parturition in indomethacin-treated sows returns normal rapid delivery and live birth (*Figure 16.5*). Since $PGF_{2\alpha}$ stimulates release of oxytocin in pigs (Ellendorff *et al.*, 1979) and oxytocin has been shown to stimulate uterine production of prostaglandins (Chan, 1977; Mitchell and Flint, 1978; Mitchell, Flint and Turnbull, 1975), their interrelationship may have a cascading effect on the development of uterine contractions.

Relaxin has been shown to have an inhibitory effect on uterine activity (Porter, 1979) and the increasing levels of relaxin near parturition (Sherwood *et al.*, 1975) may thus serve as a supplementary regulatory mechanism preventing the uterus from contractions until delivery is due.

Termination of progesterone production

Since in the pig progesterone is the principal factor maintaining pregnancy (Coggins, Van Horn and First, 1977; First and Staigmiller, 1973) and corpora lutea are the main source of progesterone (Nara, 1979; Nara, Darmadja and First, 1981), termination of luteal production of progesterone (functional luteolysis) is necessary before parturition can occur. Prostaglandin $F_{2\alpha}$ has been implicated as the uterine luteolytic agent during the oestrous cycle and exogenous $PGF_{2\alpha}$ has induced parturition. Parturition occurred approximately 30 hours after initiation of a 9–10 hour infusion of 2–5 mg of $PGF_{2\alpha}$ (Nara and First, 1981a,b; Nara, 1979), and after an intramuscular injection of 10–12 mg of $PGF_{2\alpha}$ (see *Table 16.1*). The induced parturition resulting from $PGF_{2\alpha}$ treatment is preceded by a rapid decline in plasma progesterone from 10–19 ng/ml to 3–4 ng/ml at the time of parturition (Coggins, 1975; Coggins, Van Horn and First, 1977; Diehl *et al.*, 1974; Nara, 1979; Nara and First, 1981b; Wettemann *et al.*, 1977).

Proof that $PGF_{2\alpha}$ is a natural luteolytic agent at term comes from an experiment (Nara and First, 1977; 1981b) in which the increase of $PGF_{2\alpha}$ metabolite, together with luteolysis (decrease in progesterone) and parturition, were prevented by inhibiting prostaglandin synthesis with indomethacin (*Figure 16.6*). Exogenous $PGF_{2\alpha}$ replaced the inhibited endogenous production and caused a progesterone decline and parturition. Additionally, $PGF_{2\alpha}$ metabolite was shown to be increased in the sow's blood at the same time as the decline in progesterone. A dual role of $PGF_{2\alpha}$ in causing parturition was shown in indomethacin-treated sows by the fact that low doses of $PGF_{2\alpha}$ caused luteolysis but very high doses of $PGF_{2\alpha}$ were required following infusion of the initial low luteolytic dose for normal rapid delivery of the piglets.

The key role of endogenous $PGF_{2\alpha}$ in the mechanism causing prepartum luteolysis is emphasized by the fact that dexamethasone induces luteolysis and parturition in swine through stimulation of $PGF_{2\alpha}$ synthesis (Nara, 1979; Nara and First, 1978; 1981a). In this study (*Figure 16.8*), sows treated with dexamethasone had a premature increase in $PGF_{2\alpha}$ metabolite, with a premature decrease of progesterone and the induction of

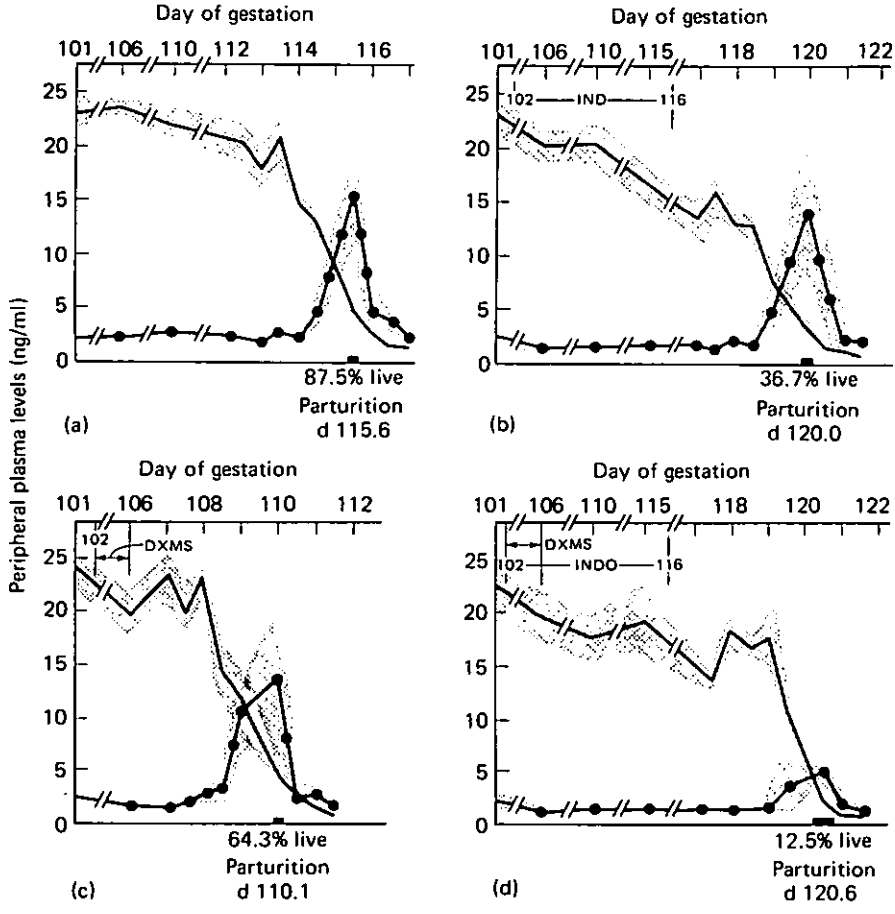

Figure 16.8 Peripheral plasma concentrations ±S.E.M. (shaded areas) of progesterone (——) and $PGF_{2\alpha}$ metabolite (—●—), percentage of live births (% live), duration of parturition (■) and length of gestation in sows receiving the following treatments (each, n = 5): (a) Control: vehicles of indomethacin and dexamethasone; (b) Indomethacin: 3 mg/kg twice daily from days 102–116 + vehicle of dexamethasone; (c) Dexamethasone: 75 mg/sow twice daily from days 102–106 + vehicle of indomethacin; (d) Indomethacin + dexamethasone: combination of treatments (b) and (c). Pre-term administration of dexamethasone caused a premature rise in plasma concentration of $PGF_{2\alpha}$ metabolite and a decline in progesterone as well as pre-term delivery. Indomethacin prevented a rise in plasma concentration of $PGF_{2\alpha}$ metabolite, a decline in progesterone and early delivery. It also prevented dexamethasone from inducing these parturient changes. From Nara and First (1981a)

parturition. The dexamethasone-induced increase in $PGF_{2\alpha}$ metabolite, progesterone decline and premature parturition were prevented when the sows were also treated with indomethacin.

This luteolytic agent at term comes from the uterus, because hysterectomy at day 112 prolongs the life of old corpora lutea and new corpora lutea that have been induced about one week before the expected term (Bosc, du Mesnil du Buisson and Locatelli, 1974). This agent travels from the uterus to the ovaries at least in part by a systemic route, since

parturition occurred after the ovaries were transplanted to the body wall in late pregnancy (Torres, 1975; Martin, Bevier and Dziuk, 1978).

These are the maternal endocrine changes known to precede and accompany parturition. The initiation of these pre-partum maternal endocrine changes is controlled by the foetuses through a sequence of events controlled by the developing foetal endocrine system.

Role of the foetuses in initiation of parturition

The way in which foetal pigs control the initiation of parturition is not completely understood, but evidence that they do is most convincing.

The source of the impetus for parturition in the pig is the foetal brain, since decapitated (Stryker and Dziuk, 1975; Coggins and First, 1977), or hypophysectomized (Bosc, du Mesnil du Buisson and Locatelli, 1974) pig foetuses will not initiate parturition.

This is similar to the situation in sheep, in which foetal pituitary ablation prevents initiation of parturition (Liggins, Kennedy and Holm, 1967), but unlike the situation in primates. Although anencephaly in human foetuses (Honnebier and Swaab, 1973) or decapitation of rhesus monkey foetuses (Novy, Walsh and Kittinger, 1977) increases variation in gestation lengths, the mean gestation length remains normal. Only one intact pig foetus in an otherwise empty uterus can initiate parturition, but if the ratio of decapitated to intact foetuses reaches 4:1, parturition is delayed (Stryker and Dziuk, 1975).

Several lines of evidence point to increased glucocorticoid production by the foetal adrenal as a crucial step in the process by which the foetus initiates parturition. The adrenalectomized sheep foetus does not initiate parturition (Drost and Holm, 1968; Liggins, 1969). Foetal adrenalectomy has not been done in pigs but foetal adrenal atrophy brought about by hypophysectomy (Bosc, du Mesnil du Buisson and Locatelli, 1974) or decapitation (Stryker and Dziuk, 1975) of pig foetuses *in utero* does prevent parturition at term. Parturition, accompanied by live birth and milk ejection, can be induced in the pig by administration of dexamethasone to the foetuses (North, Hauser and First, 1973) or sow (North, Hauser and First, 1973; First and Staigmiller, 1973; Hühn, Hühn and Konig, 1976; Coggins and First, 1977; Hühn, Konig and Hühn, 1978; Hühn and Kiupel, 1979). In addition, exogenous adrenocorticotrophic hormone (ACTH) given to the pig foetuses in the last 10 days of gestation causes hypertrophy of the foetal adrenal cortex, followed by premature parturition (Bosc, 1973).

The classic pituitary ablation/ACTH replacement experiment has not been done in the pig. Jones *et al.* (1978) hypophysectomized four foetal sheep at days 110–118 of gestation, and then infused them with Synacthen (synthetic ACTH) starting 7–16 days later. Delivery occurred within 77–112 hours of the start of infusion, almost three weeks before normal term. Here again, the mechanisms operating in the pig appear similar to those in the sheep, in which ACTH or glucocorticoids will induce pre-term parturition (Liggins, 1968), but dissimilar to those in humans, in which glucocorticoids will not induce pre-term labour (Liggins and Howie, 1972).

The porcine foetal adrenal greatly increases its capacity for glucocorticoid production late in gestation. Foetal adrenal weight increases along with increased foetal plasma cortisol levels (see *Figure 16.4*; Bosc, 1973; Fevre, Terqui and Bosc, 1975). In the sheep, most of the increase in adrenal weight is due to enlargement of the adrenal cortex, particularly the zona fasciculata (Durand, Bosc and Niedle, 1978). Recent studies in our laboratory have shown that this is also the case in the pig. Although some increase in cortex cell size occurs, most of the increase in adrenal cortex size is due to an increase in cell number, and many mitotic figures appear in the adrenal cortex at day 110 and later (*Figure 16.9*). The porcine foetal

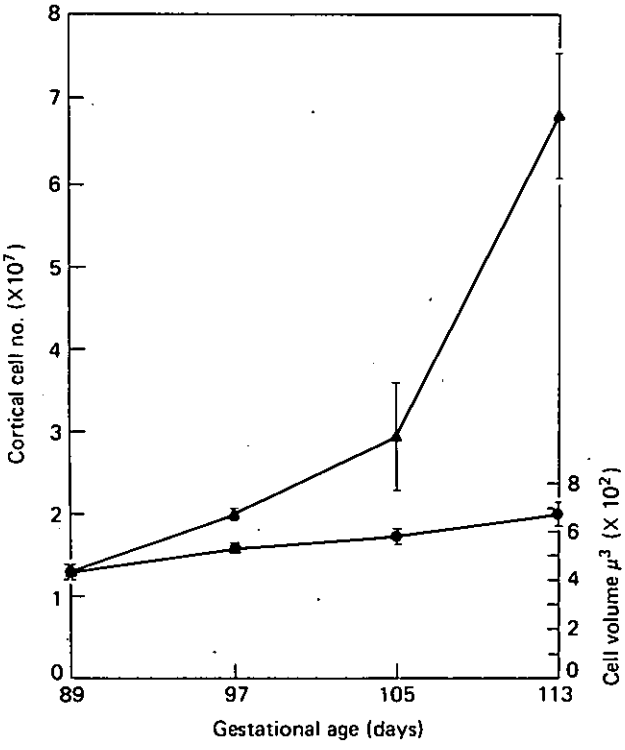

Figure 16.9 The effect of gestational age on the number and size of porcine foetal adrenal cortical cells. Each data point represents the mean ±S.E.M. of adrenal cortical cell number or volume from the paired adrenals of two foetuses from each of four litters. From Lohse and First (1981)

adrenal cortex also acquires adult type zonation and vascularity around day 110 (Lohse and First, 1981). In the light of these histological changes, ultrastructural changes were expected similar to those reported in the sheep by Robinson, Rowe and Wintour (1979). Surprisingly, in the porcine foetal adrenal, at least as early as day 89, mitochondria, smooth endoplasmic reticulum, and lipid droplets characteristic of the mature, active adrenal cortex were consistently present (Lohse and First, 1981; *Figure 16.10*).

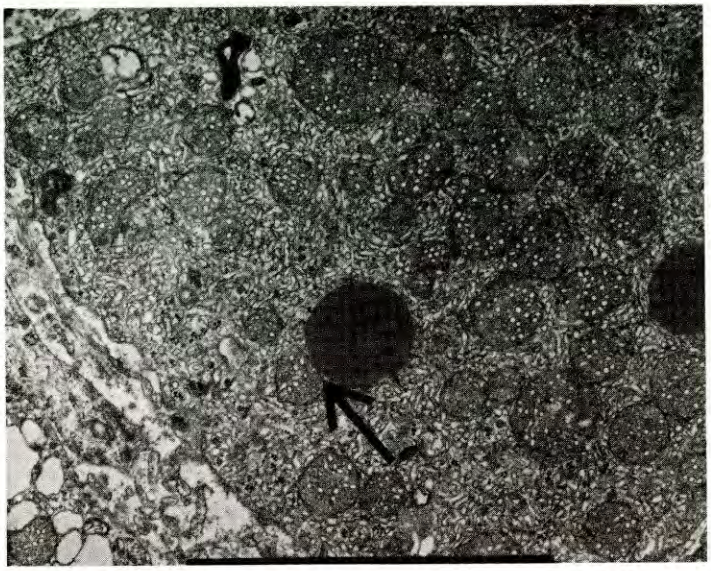

Figure 16.9 Electron micrograph of the adrenal cortex of a foetus at day 89 of gestation × 12000 (reduced to two-thirds in reproduction). Note the abundant smooth endoplasmic reticulum, typical adrenal cortex-type mitochondria and lipid droplets. Note also area of contact between lipid droplet and mitochondrion (arrow). From Lohse and First (1981)

The porcine foetal adrenal also increases its capacity for cortisol production *in vitro* as term approaches. Dvorak (1972) measured fluorogenic steroid production by adrenal tissue from late term foetal, neonatal and young pigs *in vitro* in the presence of 0.5 units ACTH/ml. This steroid production *in vitro* reached a peak at term along with foetal plasma cortisol and the ratio of adrenal weight to foetal weight. We have confirmed and expanded on the report of Dvorak (1972). Fluorogenic steroid production by porcine foetal adrenal tissue from days 89, 97, 105 and 113 of gestation was measured *in vitro* with or without 0.5 units ACTH/ml. Although the main effects of age and ACTH were both significant ($P<0.0001$), their interaction was not; the response ratio (+ACTH/—ACTH) was the same at all ages examined (*Figure 16.11*; Lohse and First, 1981). Since this result disagreed with analogous studies in the sheep (Wintour *et al.*, 1975), the dose-response to ACTH of porcine foetal adrenal tissue *in vitro* was further investigated. The same four ages were used, and following a 40 minute pre-incubation period, the tissue was incubated with 0, 1, 10 or 100 mu ACTH/ml. Although the effect of treatment on fluorogenic steroid production was again significant ($P<0.0001$), with significant increases between 0 to 1, and 1 to 10 mu/ml, the dose-response curves were the same for all ages examined. Foetal pituitary homogenate was also tested in this study, and its effects at all ages on fluorogenic steroid production was the same as that of a maximally effective dose of ACTH (Lohse and First, 1981).

This evidence that the foetal pituitary adrenal axis is functional well before the pre-partum cortisol surge is supported by earlier work from our

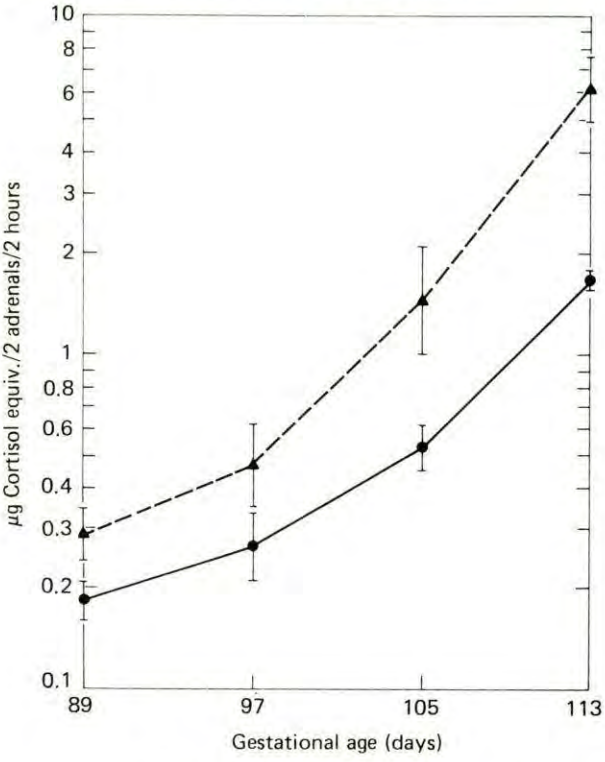

Figure 16.11 The effect of ACTH and foetal age on the *in vitro* production of adrenal fluorogenic steroids; -▲--▲- 500 mu ACTH/ml, —●—●— buffer only. The data represent the mean ±S.E.M. of the logs of μg cortisol equivalents of fluorogenic steroids produced by the adrenals of a foetus during 2 hours of incubation. Each data point is derived from two foetuses of each of four litters. From Lohse and First (1981)

laboratory. North, Hauser and First (1973) found that dexamethasone injected into foetal pigs on day 102 of gestation lowered foetal adrenal weights, probably through a negative feedback effect on pituitary corticotrophin. Hühn and Kiupel (1979) reported a suppression of foetal adrenal weight at parturition induced by administration of dexamethasone to the sow. Unlike North, Hauser and First (1973), however, these investigators did not adjust for the reduced birthweight of those piglets whose premature birth was induced by dexamethasone.

Because the fluorogenic steroid assay does not distinguish between cortisol and corticosterone, and since earlier studies (Madill and Bassett, 1973; Wintour *et al.*, 1975) reported a change with gestational age in the proportions of steroid produced by the foetal sheep adrenal, samples from each age that had been incubated with 0 or 100 mu ACTH/ml or with foetal pituitary homogenate were subjected to steroid separation and analysis by high pressure liquid chromatography (HPLC). No change in steroid proportions was observed until day 113, when there was a large increase in the relative proportion of cortisol (*Figure 16.12*; Lohse and First, 1981).

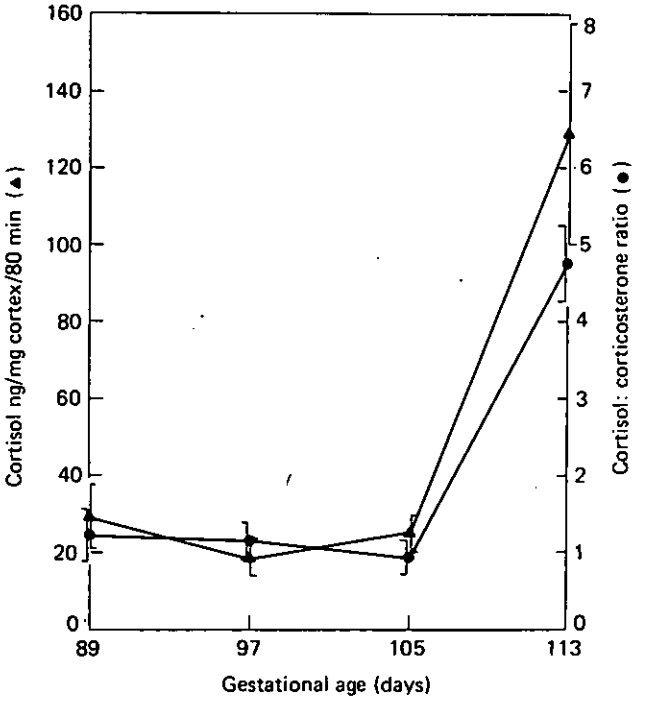

Figure 16.12 The effect of gestational age on the production *in vitro* of cortisol and the cortisol:corticosterone ratio of porcine foetal adrenals. Each data point is derived from the mean ±S.E.M. of two litters in which both adrenals of all piglets in the litter were incubated and the data pooled to provide a value for a litter. From Lohse and First (1981)

Consideration together of results from the various parts of this study suggests that increased adrenal cortex weight, due primarily to increased mitosis, accounts for the increase in cortisol production from days 89–105, but not from days 105–113. It was between days 105 and 113 that the change in steroid ratios occurred (*Figure 16.12*).

The means by which the foetal brain controls the foetal adrenal is not yet completely known. Although ACTH can bring about adrenal hypertrophy and parturition in the last 10 days of gestation, it is not usually associated with the hyperplasia that was observed in the late term foetal adrenal. Some other hormonal and/or neural factors may be involved as well. In addition, even if ACTH is the sole means by which the foetal brain controls the foetal adrenal, what controls foetal ACTH? If foetal ACTH secretion is regulated by foetal hypothalamic corticotrophin releasing factor (CRF), what controls foetal CRF secretion? To further complicate matters, control of adrenal cortisol production by the foetal pituitary may not be the only way the foetal brain regulates steps in the induction of parturition. Parturition in pigs was not induced by maternal administration of dexamethasone until after day 100 of gestation (Coggins, 1975; *Table 16.2*) and dexamethasone injected after day 100 was incapable of inducing parturition when foetuses were decapitated (Coggins and First, 1977). Adrenocorticotrophic hormone given to the foetuses also failed to induce

Table 16.2 EFFECT OF TREATMENT WITH DEXAMETHASONE AT DIFFERENT STAGES OF GESTATION ON LENGTH OF GESTATION

	Day of gestation at start of treatment[a]				
	81	*91*	*101*	*Control*	*S.D.*
No. of sows	4	4	4	4	
Gestation length (days)[b]	116.3	115.3	109.7	115.8	1.75

[a]100 mg of dexamethasone/day injected intramuscularly on four consecutive days (adapted from Coggins, 1975)
[b]Means not significantly different from each other are underlined; day 101 group different ($P<0.05$)

parturition until day 100 (Bosc, 1973). These facts imply that a parallel or later step, perhaps a target for the glucocorticoids, must be developed before dexamethasone can induce parturition. This step, like increased foetal adrenal glucocorticoid secretion, depends on the foetal brain.

The concept of the placenta as the target organ for the pre-partum glucocorticoid action is supported by studies in sheep and rabbits. In sheep, the source of pregnancy-maintaining progesterone is the placenta (Linzell and Heap, 1968). Before either spontaneous or glucocorticoid-induced parturition, progesterone levels decline, 17,20α-dihydroxy-4-pregn-3-one (17,20αP) levels increase, and oestrogen levels increase (Flint *et al.*, 1975). Placental minces taken at these times increase their metabolism of ^{3}H-pregnenolone to 17,20αP at the expense of progesterone (Anderson, Flint and Turnbull, 1975).

There also appears to be an increase in C-17,20-lyase activity *in vitro* in ovine placental tissue collected following endogenous or exogenous glucocorticoid elevation (Steele, Flint and Turnbull, 1976a). This is confirmed by a reported rise in uterine androstenedione production at parturition (Steele, Flint and Turnbull, 1976b). It has been suggested (Flint, Ricketts and Craig, 1979) that this increased conversion of C-21 to C-19 steroids may be a result of decreased placental progesterone concentration, since progesterone inhibits C-17,20 lyase in some tissues. The possibility that the foetal or maternal adrenals are the source for pre-partum aromatizable androgens has been ruled out by adrenalectomy experiments (Flint *et al.*, 1976; Flint and Ricketts, 1979) and by the lack of effect of hypoxic stress on maternal or foetal androgen levels (Jones *et al.*, 1977).

The importance of placental participation in parturition has been demonstrated by a study in the rabbit, in which the close connection between the placenta and endometrium permits the placenta to be maintained in the absence of a foetus. When foetuses were removed on or before day 25 of gestation, parturition at term did not occur and could not be induced by dexamethasone. When foetuses were removed on or after day 26, the placentas were delivered at normal term on day 32 (Chiboka, Casida and First, 1977). Unfortunately, complete foetectomy in the pig results in prompt abortion (Chiboka, Casida and First, 1976).

It seems apparent from the studies of Nara and First (1978; 1981a) that in the pig glucocorticoids induce parturition by causing an increase in uterine $PGF_{2\alpha}$ secretion, which in turn brings about luteolysis. The mechanism by which glucocorticoids elevate $PGF_{2\alpha}$ secretion has not yet been worked out. In the sow, plasma oestrogens (Robertson and King,

1974) and urinary oestrogens (Rombauts, 1962) increase considerably in late gestation. The source of these oestrogens appears to be intrauterine, since neither ovariectomy, hypophysectomy (Fevre, Leglise and Rombauts, 1968) nor adrenalectomy (Fevre, Leglise and Reynaud, 1972) of pregnant sows alters the pattern of oestrogen excretion during pregnancy. Also, the amount of urinary oestrogens is proportional to litter size and drops off sharply following parturition (Fevre, Leglise and Rombauts, 1968).

Oestrogens stimulate the release of $PGF_{2\alpha}$ by the gravid uterus and can be used to induce parturition in the sheep (Currie, 1977; Liggins *et al.*, 1973; 1977) and goat (Currie and Thorburn, 1973). However, in three different studies, large doses of oestrogen to the sow (B.S. Nara and N.L. First, unpublished; Nellor *et al.*, 1975; Flint, Ricketts and Craig, 1979) or the foetuses (*Table 16.3*) failed to induce parturition. Exogenous oestrogen

Table 16.3 EFFECT OF INTRAMUSCULAR INJECTIONS OF OESTRADIOL CYPIONATE (OCP) IN COTTONSEED OIL (CSO) ON PREGNANT PIGS[a]

OCP dose (mg/day)	*Days of gestation injected*	*No. sows*	*Gestation length* (days)	*Live births* (%)	*Litter size*	*Onset of lactation*
Maternal application:						
50	103–105	4	115.5±0.6	92.1±5.9	9.3±1.9	4/4
25	110–pt.[b]	4	115.8±0.5	96.1±3.8	8.8±1.4	4/4
0 (CSO 15 ml)	80–97	5	115.8±0.4	94.4±3.4	7.6±1.7	5/5
15	80–97	4	115.0±0.4	88.6±11.4	9.0±1.2	4/4
0 (CSO 15 ml)	90–107	5	115.2±0.9	87.7±6.4	7.6±1.7	5/5
15	90–107	5	113.8±0.6	95.6±2.9	11.2±1.4	5/5
Fetal application:						
6 foetuses/litter 2.5 mg/foetus (15 mg total)	103	4	112.5±1.7	78.6±21.4	6.8±0.9	4/4
2.5 ml CSO/foetus (0 mg total)	103	4	111.5±2.1	77.9±15.0	8.5±1.6	4/4

[a]Adapted from Nara, 1979: No significant effects were detected among treatments with either maternal or foetal application of oestradiol cypionate.
[b]pt = parturition.

administration may be ineffective in the pig in the last 35 days of gestation, since circulating oestrogens in the sow are quickly inactivated by conjugation at this time (Rombauts, 1962). The effect of infusion of oestrogen into the placental circulation has not been examined.

Another surprising change in porcine placental steroid metabolism is an apparent increase in progesterone production at delivery, as indicated by foetal and umbilical venous progesterone levels at birth (Silver *et al.*, 1979).

Although the exact mechanisms by which increased foetal cortisol elevates uterine $PGF_{2\alpha}$ production and by which the foetal brain controls the foetal adrenal are not yet completely understood, the available information is sufficient to formulate a model describing parturition in the pig. This proposed model is presented in *Figure 16.13*.

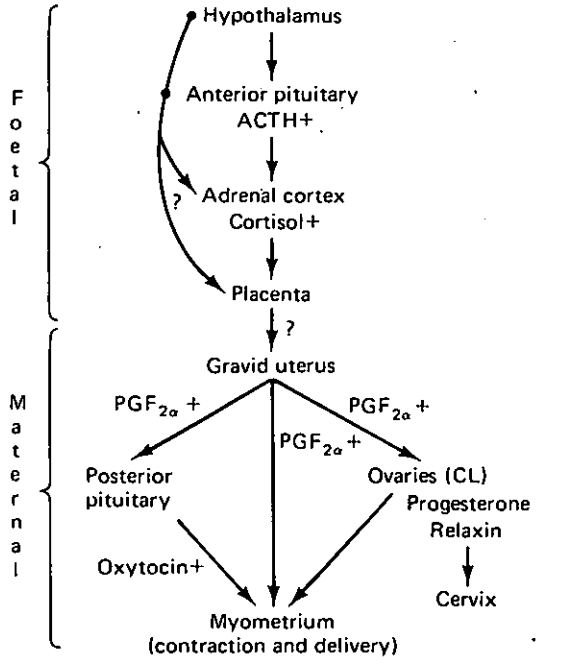

Figure 16.13 A suggested sequence of events leading to and associated with parturition in the pig. Hormones having a stimulatory effect on a target are designated with a (+); unknown steps or compounds are indicated by a (?). From First and Bosc (1979)

The induction of parturition

If the proposed model (*Figure 16.12*) for the steps and mechanisms initiating parturition is valid, it should be possible to induce parturition before term by exogenous administration of the hormonal messengers eliciting the sequence of events leading to parturition. This has been shown possible for four of the messengers: ACTH to the foetus (Bosc, 1973); cortisol analogues to foetuses (North, Hauser and First, 1973) or the mother (North, Hauser and First, 1973; First and Staigmiller, 1973; Coggins and First, 1977; Coggins, Van Horn and First, 1977; Hühn, Konig and Hühn, 1978; Hühn and Kiupel, 1979; Brenner *et al.*, 1979; Nara and First, 1981a); $PGF_{2\alpha}$ and its analogues to the mother (*Table 16.1*); and within the last 12 hours of gestation, oxytocin to the mother (Muhrer, Shippen and Lasley, 1955; Welk and First, 1979).

This knowledge has provided the basis for the development of methods for the induction of parturition. The potential benefits derived from the ability to induce parturition at a precise time are:

(a) more efficient use of farrowing facilities and labour,
(b) avoidance of parturition on weekends, holidays or at late hours of the night,
(c) more efficient cross-fostering of litters,

(d) more uniformity in the time of oestrus for lactating sows after weaning and in the age and weight of piglets in feedlots, and
(e) reduction in the length of gestation.

Unfortunately, the latter is of limited feasibility. Attempts to cause delivery before day 109 have resulted in death of the piglets by day 1 post-partum (Wierzchos and Pejsak, 1976; N.L. First, unpublished). Piglets born as late as day 110 (Jainudeen and Brandenburg, 1980) or in some cases day 111 (Gilchrist-Shirlaw, Hillyer and Miller, 1978; Aumaitre, Deglaire and LeBost, 1979; Bosc and Martinat-Botte, 1976; Hammond and Carlyle, 1976) have reduced survival and reduced birth and weaning weight. However, piglets born two, and in some experiments, three days before term have normal survival and normal birth and weaning weights (Aumaitre, Deglaire and LeBost, 1979; *Table 16.1*).

Of the potential substances which might be used to induce parturition in commercial pig herds, ACTH or Synacthen, seems not to be practical for commercial use because it is effective only by foetal administration (Bosc, 1973; Brenner *et al.*, 1979).

Oxytocin is effective at a time when the blood plasma is nearly depleted of progesterone and after milk ejection can be elicited (Muhrer, Shippen and Lasley, 1955). At this stage, injection of 50 iu oxytocin will cause delivery within 0.6±0.6 hours (Welk and First, 1979).

The glucocorticoid dexamethasone has been used in several experiments to successfully induce parturition. While a single small dose of 6 mg to each of seven foetuses was effective (North, Hauser and First, 1973), a large dose of 75–100 mg/day for 3–4 days was required for parturition to be induced by maternal intramuscular injection (First and Staigmiller, 1973; Coggins and First, 1977; Hühn, Konig and Hühn, 1978; Hühn and Kiupel, 1979; Brenner *et al.*, 1979; Nara and First, 1981a). Besides being expensive and requiring repeated injection, there is more variation in the interval from treatment to parturition than after the injection of $PGF_{2\alpha}$.

The most effective, efficient and widely accepted method to date for inducing parturition in pigs is an intramuscular injection of $PGF_{2\alpha}$ or one of its analogues. The number of studies in which $PGF_{2\alpha}$ or its analogues has been used is far greater than can be presented in one review. *Table 16.1* represents an attempt to summarize several such studies in which similar data were collected and where untreated sows provided contemporary control data. Only data derived from doses of drugs proved to be effective and from sows treated after day 110, have been considered. There seems to be little difference in the response of sows and litters to $PGF_{2\alpha}$ or its analogues except for the magnitude of the effective dose and for the studies summarized here, a tendency for the analogues to cause more sows to farrow within 48 hours after treatment. This difference may relate more to the dose of drug used than to differences between the compounds. When both $PGF_{2\alpha}$ and cloprostenol were compared in the same experiment, there was no difference (Boland, Craig and Kellcher, 1979).

Approximately 87% of sows injected after day 110 with $PGF_{2\alpha}$ or 93–100% with its analogues farrowed within 48 hours. The average time from injection to delivery of the first piglet was approximately 28±5.5 hours for $PGF_{2\alpha}$ and 26.4±5.7 hours for cloprostenol, the most commonly used analogue of $PGF_{2\alpha}$. Why parturition is not induced in some sows is

unknown. It may be pertinent that all are induced when $PGF_{2\alpha}$ is infused intravenously for 10 hours (Nara and First, 1981a,b). Additionally, some investigators found that sows not responding to the injected $PGF_{2\alpha}$ were not pregnant (Jainudeen and Brandenburg, 1980) while others observed those not responding had an excessively long gestation period (Hansen, 1979).

When $PGF_{2\alpha}$ compounds are administered after day 110, most experiments show no significant difference between treated and control sows in duration of labour, the frequency of piglets born dead, birth weight, survival to weaning or weaning weight although the means suggest slightly greater birth weight for the controls. This seems to be the case for the data summarized in *Table 16.1*.

The interval from injection of $PGF_{2\alpha}$ compounds to the initiation of parturition is shortened when the drug is injected very close to expected parturition (Bosc and Martinat-Botte, 1976; Willemse *et al.*, 1979). This is likely to be due to the endogenous initiation of the events leading to parturition before the exogenous administration of $PGF_{2\alpha}$.

The sows return to oestrus and have normal post-weaning reproductive performance after the induction of parturition (Bosc and Martinat-Botte, 1976; Walker, 1979; Lynch and Langley, 1977; Robertson, King and Elliott, 1978).

Prostaglandin $F_{2\alpha}$ may not be the only prostaglandin capable of inducing parturition. Of considerable interest is the recent study of Vaje *et al.* (1980) in which parturition was induced on day 110 by intravenous infusion for 10 hours on day 109 of a prostaglandin E analogue, sulproston, or 47±11 hours after two intramuscular injections of sulproston. How this is accomplished is unknown.

The distribution of sows farrowing after injection of $PGF_{2\alpha}$ compounds is compared with control sows in *Figure 16.14*. While most sows farrow on one day (~70%), those which do not complicate the management of a farrowing unit and reduce the benefits of induced parturition.

There have been two attempts to develop methods for making the time of prostaglandin-induced parturition more precise. When oxytocin was injected on the expected day of cloprostenol-induced parturition and at a time when milk could be ejected, the interval from injection of prostaglandin to delivery of the first piglet was 27.7±2 hours and the variance in time of delivery was significantly reduced from that due to cloprostenol alone (Welk and First, 1979). This combination of drugs allows synchronization and supervision of farrowings during a specified half day.

In a second attempt, the treatment involved the daily administration of 100 mg of progesterone on days 112, 113 and 114, accompanied by 200 µg of cloprostenol on day 115 (Gooneratne *et al.*, 1979). 80% of the sows farrowed between 08.00 and 17.00 on day 116 and a precise time of parturition, 25.4±1 hour, after injection of cloprostenol was achieved. Although this study was without a control group in which cloprostenol alone was used, the initiation of lactation, piglet survival and weight, and post-partum reproductive performance of the sow were not different from untreated controls.

The frequency of sows showing prolonged elevation of body temperature or clinical symptoms of the Metritis–Mastitis–Agalactia (MMA)

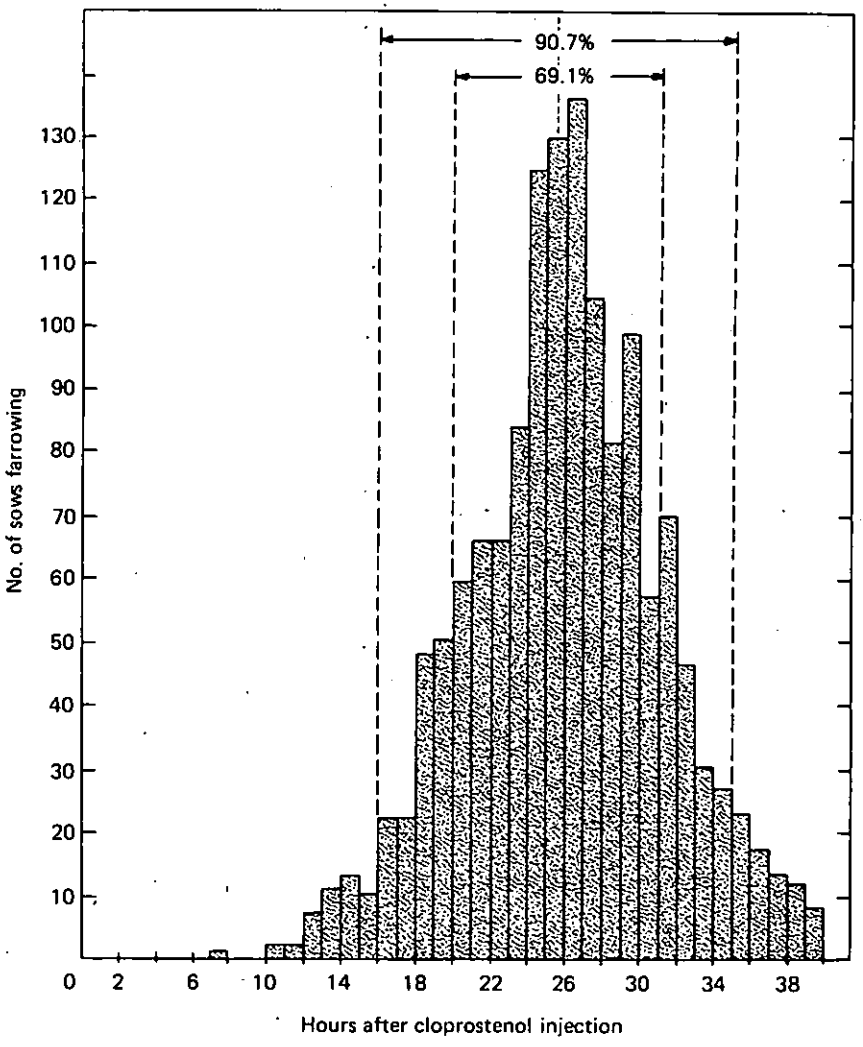

Figure 16.14 Distribution of 1459 sows farrowing at specific times after a single intramuscular injection of 175 μg cloprostenol. Approximately 69% commenced farrowing between 20 and 30 hours and 90.7% between 16 and 34 hours after treatment. From Hammond and Matty (1980)

syndrome has been reported in several studies to be less after the induction of parturition than for control sows (Einarsson, Gustafsson and Larsson, 1975; Backstrom *et al.*, 1976; Ehnvall *et al.*, 1976; Hansen and Jacobsen, 1976; Bogataj, 1979; Humke, Seidel and Scharp, 1979; Hühn, Lutter and Hühn, 1980). A slight difference in the same direction is evident from the studies summarized in *Table 16.1*. Whether this is a consistent benefit from the induction of parturition or mainly reported by investigators finding a difference remains to be determined. Some have found no reduction in the frequency of MMA after induction of parturition (Hansen, 1979; Samol, 1980).

The ultimate value of $PGF_{2\alpha}$ or its analogues as agents for induction of parturition is enhanced by the fact that these compounds induce a normal parturition as well as a series of parturition-related events including initiation of lactation and expulsion of the placenta (First and Bosc, 1979). Whether the induction of parturition will become a widely accepted pig management tool remains to be determined.

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