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Control of Parturition in the Sow using Progesterone and Prostaglandin

Anoma Gooneratne, P. E. Hartmann, I. McCauley and C. E. Martin

Department of Biochemistry,
University of Western Australia,
Nedlands, W.A. 6009.

Abstract

The effect of progesterone and prostaglandin administration on the timing of farrowing was studied in three groups of 25 sows each. Progesterone treatment (100 mg/day) on days 112, 113 and 114 of gestation (group I) significantly prolonged the gestation length to $116 \cdot 4 \pm 0 \cdot 4$ (mean $\pm$ s.e.) days compared to the control sows (group III; $115 \cdot 5 \pm 0 \cdot 2$; $P < 0 \cdot 05$). Administration of prostaglandin (200 μg Cloprostanol intramuscularly) on day 115 of gestation following progesterone treatment (group II) resulted in a gestation length of $116 \cdot 0 \pm 0 \cdot 1$ days, with the sows farrowing $25 \cdot 4 \pm 1 \cdot 0$ h after the prostaglandin injection. 80% of the sows farrowed between 0800 and 1700 h of day 116 of gestation.

Plasma progesterone levels were maintained by the exogenous progesterone during treatment. At farrowing, higher levels of progesterone were observed in groups I and II compared to controls. Prostaglandin treatment did not significantly alter withdrawal of progesterone in progesterone treated sows, suggesting that the actions of exogenous prostaglandin is primarily on the myometrium and the cervix.

Hormonal treatment in late pregnancy did not have any adverse effects on piglet viability and growth rate, or subsequent reproductive performances of sows. Lactation was initiated normally, and the concentrations of lactose, protein, fat, IgG, Na^+, Ca^{2+} and K^+ in colostrum and milk were similar in all groups during the first 5 days of lactation.

Introduction

The onset of parturition in several mammalian species is preceded by a sequence of endocrine changes of both maternal and foetal origin. The endocrine changes include the withdrawal of progesterone from the maternal circulation and an increase in the concentration of prostaglandins in the utero-ovarian vein (Liggins *et al.* 1977; Heap *et al.* 1977). The involvement of both progesterone and prostaglandin $F_{2\alpha}$ in the initiation of parturition in the sow (Thorburn *et al.* 1977) has led to various investigations of the administration of these compounds to control the time of farrowing. Exogenous progesterone has been used to delay farrowing in sows (First and Staigmiller 1973; Coggins *et al.* 1977; Sherwood *et al.* 1978). However, in all circumstances foetal mortality was increased. Furthermore, Sherwood *et al.* (1978) observed that in sows in which farrowing was delayed by the administration of progesterone, lactation initiated at the time normal farrowing was expected to occur. Commercially acceptable synchronization of farrowing has been achieved using either prostaglandin $F_{2\alpha}$ or its analogues (Ash and Heap 1973; Hendricks and Handlin 1974; Downey *et al.* 1976). This procedure necessitates the synchronization

of farrowing some 4–5 days before normal term, and thereby results in lowered birth weights of piglets (Wettemann *et al.* 1977).

The present study investigates the possibility of providing a more flexible control over the time of farrowing by treating sows with a combination of progesterone and prostaglandin $F_{2\alpha}$.

Materials and Methods

Animals

Sows (from 1st to 8th gestation Landrace, Large White and Landrace × Large White) were housed under intensive management in a commercial piggery (Baconfield Piggery, Bullsbrook, W.A.). The sows were brought into individual farrowing crates 1 week before the expected date of farrowing, and maintained in the crates until weaning (3–4 weeks *post partum*).

Progesterone and Prostaglandin Treatment

Sows were chosen at random, subdivided into three groups and assigned the following treatments.

Group I (GI): 25 sows received 100 mg/24 h progesterone [Sigma, 25 mg/ml in peanut oil, intramuscularly (i/m)] from day 112 through to day 114 of gestation. On day 112 the total dose was injected between 0900 and 1000 h, whereas on days 113 and 114 of gestation, the progesterone was given in two equal doses between 0900–1000 h and 2100–2200 h.

Group II (GII): 25 sows were given the progesterone treatment as for group I, followed by an injection of a synthetic analogue of prostaglandin, cloprostanol (PG; 200 μg Estrumate, I.C.I., i/m) at 1000 h on day 115 of gestation.

Group III (GIII): 25 sows were treated similarly to group I except that they received a placebo of peanut oil alone.

Reproductive Observations

The following data were recorded for all three groups:

(1) Gestation length and time of farrowing;
(2) Litter size and weight at birth and at 19 days of age;
(3) Return to oestrus after weaning.

Blood Samples

Blood samples (1–2 ml) were obtained by venepuncture from the ear vein of tethered but otherwise unrestrained sows. Samples were collected at approximately 0900 h daily, from day 112 of gestation and continued until 3 days *post partum*. From day 114 of gestation through to the day of farrowing an additional sample of blood was taken at 2100 h. The blood was immediately heparinized and plasma separated by centrifugation and stored at −15°C until assay.

Blood samples were obtained from 10 sows each from groups I and III and from 7 sows in group II.

Plasma Analysis

Plasma progesterone concentrations were measured by a modification of the protein binding assay described by Martin *et al.* (1977). The recovery of [^{3}H]progesterone from plasma samples was estimated at various times with different batches of hexane fraction (Unilab, Ajax Chemicals Ltd., Sydney). No differences were observed and the recovery was $96 \cdot 8 \pm 1 \cdot 8\%$ (mean ± s.e., $n = 20$).

Colostrum and Milk Samples

Colostrum was obtained from the sows (three sows from each group) at farrowing or within 3 h of farrowing by manual expression, and each sow was sampled daily (between 0900 and 1000 h) for the next 5 days. Between 1–5 ml of mammary secretion was collected separately from the four

most anterior glands (left and right), and frozen immediately for subsequent analysis. For the first 2 days *post partum* milk was collected after milk let down was initiated by stimulation of the udder by the piglets. Thereafter, milk ejection was accomplished by intravenous injection of 1 i.u. of oxytocin (Pitocin, Parke Davis and Co.).

Analysis of Mammary Secretion

(i) *Lactose*

The concentration of lactose in milk was measured by the method of Kuhn and Lowenstein (1967).

(ii) *Protein*

The milk protein content was estimated by the method described by Johnson and Lott (1978) using the dye Coomassie Brilliant Blue G250.

(iii) *Fat*

Milk fat was estimated as total esterified fatty acids (Hartmann 1973) assuming the mean molecular weight of sow milk fatty acids to be 266 (De Man and Bowland 1963).

(iv) *Ion determinations*

Ca^{2+}, Na^+ and K^+ determinations were carried out on a Varian Techtron atomic absorption spectrophotometer model 1200. Ca^{2+} was determined by diluting the milk 1:500 in as olution containing 1·0 g/l lanthanum (as $LaCl_3.7H_2O$). Na^+ and K^+ were determined by first extracting the milk fat with ether (milk:ether 1:1 v/v) and then diluting the skim milk 1:1000 in a solution of 1·0 g/l caesium (as CsCl).

(v) *Immunoglobulins*

Antiserum to swine IgG was raised in rabbits and prepared by the method of Porter (1969). This antiserum was absorbed with pure swine IgA coupled to Sepharose 4B (Pharmacia, Uppsala) and was monospecific when tested by immunoelectrophoresis and double diffusion analysis against purified immunoglobulins, serum, colostrum and milk. The concentration of IgG in milk samples (diluted between 5- and 200-fold) was determined by single radial immunodiffusion (Mancini *et al.* 1965) with reference to purified IgG standards.

Statistical Analysis

All results were analysed statistically using one-way analysis of variation and Student *t*-test (Snedecor and Cochran 1972).

Results

Gestation Length

The gestation length for the control group of sows (GIII) ranged between 114 and 119 days (mean$\pm$s.e. 115·5$\pm$0·2, Fig. 1). Treatment with progesterone (GI) prolonged the gestation length to 116·4$\pm$0·4 days ($P<0·05$), and restricted the farrowing period to 3 days (116–118 days of gestation).

The sows receiving a single injection of PG following progesterone treatment (GII) had an extended gestation length of 116·0$\pm$0·1 days ($P<0·001$). The average time taken to farrow after the PG injection was 25·4$\pm$1·0 h (range 9–44 h) and 80% of these sows farrowed between 0800 and 1700 h on the 116th day of gestation. Furthermore, the time interval between the final progesterone treatment and the onset of

parturition was reduced significantly ($P<0{\cdot}005$) from $48{\cdot}5\pm3{\cdot}0$ h to $36{\cdot}6\pm1{\cdot}0$ h by the administration of PG.

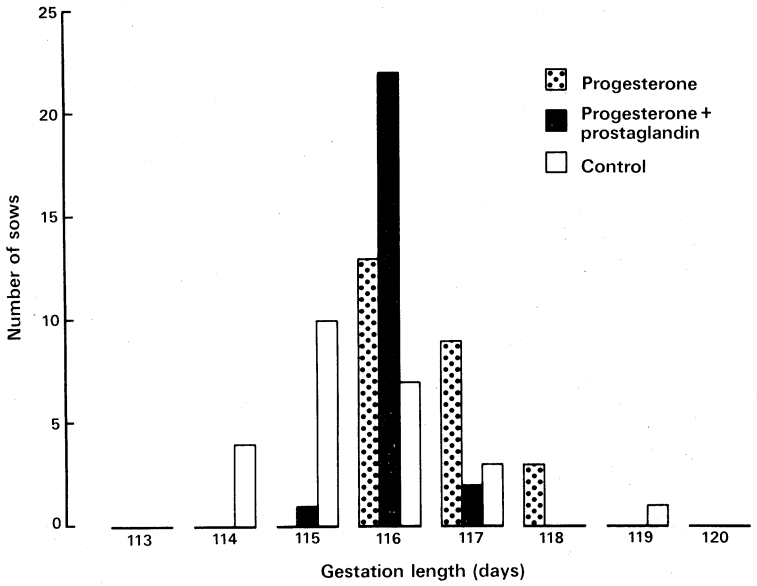

Fig. 1. Gestation lengths of sows treated with progesterone (GI) and with progesterone plus prostaglandin (GII) and of control sows (GIII).

Litter Size and Weight

There was no significant difference in litter size and weight of piglets between the three treatment groups either at birth or at 19 days age (Table 1).

Table 1. Litter sizes and weights at birth and at 19 days of control sows and of sows treated with progesterone (P) and with progesterone plus prostaglandin (P+PG)

Treatment	Group	Mean litter size±s.e.		Mean litter weight (kg)±s.e.	
		At birth[A]	At 19 days	At birth	At 19 days
P	GI	9·30±0·5 (1·36±0·3)	8·92±0·4	13·03±0·7	37·79±1·4
P+PG	GII	9·16±0·5 (1·00±0·4)	8·24±0·5	13·64±0·7	36·85±1·3
Control	GIII	9·40±0·5 (0·32±0·1)	8·96±0·4	13·59±0·7	35·18±2·2

[A] Values in parentheses are numbers of still born.

Return to Oestrus After Weaning

The number of days (mean±s.e.) from weaning to first oestrus for the sows was $6{\cdot}0\pm0{\cdot}3$, $7{\cdot}0\pm1{\cdot}5$ and $11{\cdot}2\pm2{\cdot}8$ for groups I, II and III respectively. The differences between them were not significant.

Plasma Progesterone Concentration

The changes in the concentration of plasma progesterone from the commencement of treatment to 3 days *post partum* are shown in Fig. 2. In the progesterone-treated sows (GI and GII) the plasma progesterone levels were maintained within the range of levels observed at 111 days gestation during the treatment period (112–114 days of gestation). The concentration of progesterone in the plasma declined before parturition in all the sows. At the time of farrowing, the concentration of progesterone in the plasma of control sows (GIII) ranged between 0·3–3·5 μg/l. In the progesterone-treated sows, higher levels of progesterone (range 3·2–17·6 μg/l) were observed at the same gestation length (i.e. 115 days gestation, Fig. 2). At farrowing, the plasma progesterone concentration in group I sows was significantly higher ($P<0·05$) than in the controls (GIII). There was no significant difference between the levels obtained for group II and either of the other groups (GI and GIII).

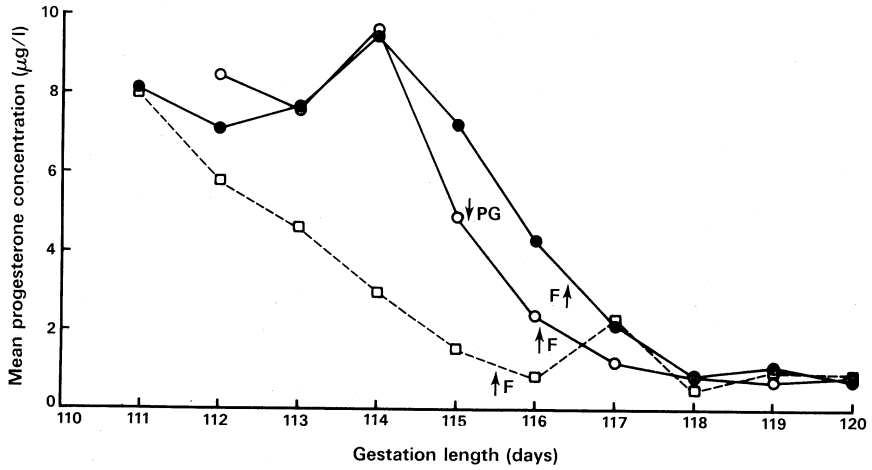

Fig. 2. Mean progesterone concentration in plasma over a period of 9 days from day 111 of gestation in 10 sows which were treated with progesterone (GI, ●), in 7 sows treated with progesterone plus prostaglandin (GII, ○), and in 10 control sows (GIII, □). Progesterone treatment: 100 mg/day on days 112, 113 and 114 of gestation. Prostaglandin treatment: 200 μg Estrumate on day 115 of gestation. ↓ PG indicates time of prostaglandin injection. ↑ F indicates mean time of farrowing for each treatment group.

Mammary Secretion

A comparison of the concentrations of various milk constituents (lactose, protein, fat, Ca^{2+}, Na^{+}, K^{+}) of the sows in each of the three treatment groups during the first 5 days of lactation is shown in Fig. 3. The mean concentration of lactose in all the sows rose sharply during the first 24 h *post partum*, and thereafter increased gradually. The concentration of protein in the mammary secretion in all three groups of sows was high at parturition, declined to almost half by 1 day *post partum*, and then decreased gradually until low values were reached by 5 days *post partum*. There was a peak in the concentration of fat on day 2 *post partum* in the milk of sows in groups I and III, but not in group II.

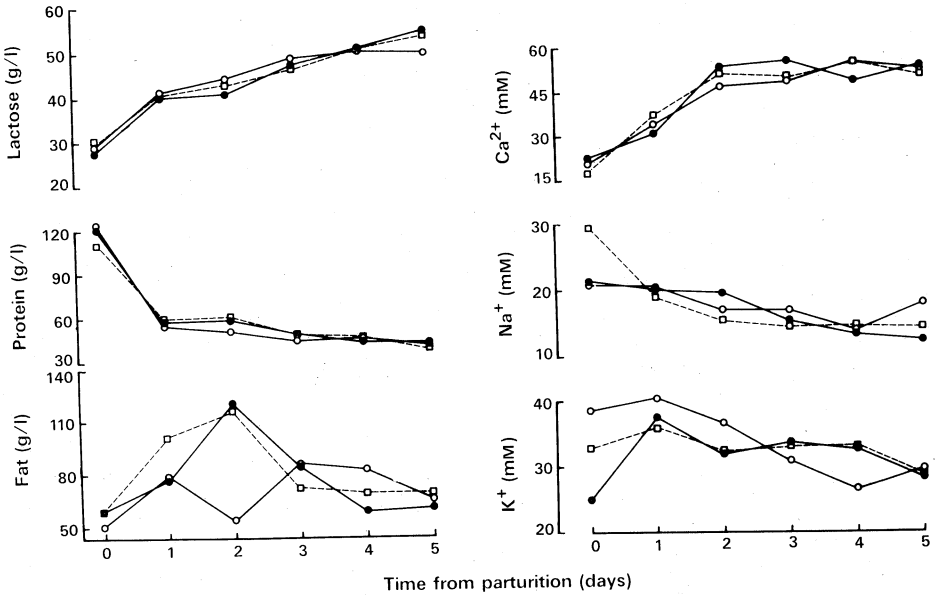

Fig. 3. Mean concentrations of lactose, protein, fat, Ca^{2+}, Na^+ and K^+ in colostrum and milk in three sows treated with progesterone (GI, ●), three sows treated with progesterone plus prostaglandin (GII, ○), and three control sows (GIII,□), during the first 5 days of lactation.

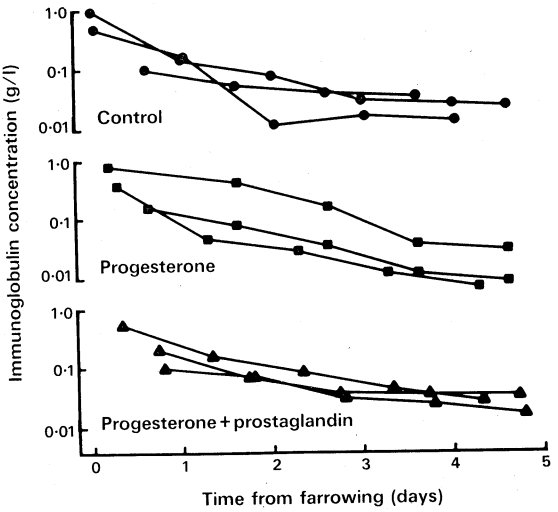

Fig. 4. Immunoglobulin concentrations in colostrum and milk in three sows treated with progesterone (GI), three sows treated with progesterone plus prostaglandin (GII), and three control sows (GIII).

The changes in the concentration of Ca^{2+}, Na^{+}, K^{+} in the mammary secretions showed similar trends in each group. Following farrowing, there was a doubling of Ca^{2+} concentration and thereafter the levels remained relatively constant. The concentration of Na^{+} decreased gradually during lactation. The concentration of K^{+} increased slightly on the first day *post partum* and then declined gradually.

The concentration of IgG in the colostrum and milk of sows in each of the three groups during the first 5 days of lactation (Fig. 4) showed no significant differences between treatments. During the first 48 h *post partum*, the levels of IgG dropped rapidly in all groups followed by a more gradual decrease.

Discussion

Although gestation length was extended by the administration of progesterone to sows in late pregnancy (First and Staigmiller 1973; Coggins *et al.* 1977; Sherwood *et al.* 1978), the foetal mortality and incidence of dystocia were increased. In contrast to these findings, the present study on larger numbers of sows (25 per treatment, compared to a maximum of four per treatment in previous studies) demonstrated that the administration of progesterone (100 mg/day) from 112 to 114 days of gestation extended the gestation length (Fig. 1) without significantly increasing foetal mortality (Table 1). It is probable that either the high dose of progesterone (up to 500 mg/day) or the prolongation of mean gestation length to $>117{\cdot}5$ days caused the increased incidence of stillbirths and dystocia in previous studies. Sherwood *et al.* (1978) administered 100 mg/day progesterone from 110 to 113 days of gestation to one treatment group but did not significantly increase either gestation length ($113{\cdot}8$ days control; $115{\cdot}7$ days test) or foetal mortality (13% control; 51% test).

Progesterone treatment to sows (GI) prevented early farrowing but did not result in a high degree of synchronization of farrowing (Fig. 1). Administration of PG at 115 days of gestation to progesterone treated sows (GII) decreased the range of farrowing time (Fig. 1) to 36 ± 1 h (mean$\pm$s.e.) after the last progesterone injection, giving an interval of $25{\cdot}4\pm1{\cdot}0$ h (mean$\pm$s.e.) after PG administration. This interval is similar to that observed for sows treated with PG alone to induce parturition (Ash and Heap 1973; Diehl *et al.* 1974; Einarsson *et al.* 1975; Downey *et al.* 1976). However, in contrast to lowered birth weights observed during premature initiation of parturition (Downey *et al.* 1976; Wetteman *et al.* 1977), there was no significant difference in birth weights between the treated groups and controls in the present study.

The concentration of progesterone declines rapidly to low levels at parturition in both normal sows (Ash and Heap 1975; Martin *et al.* 1978) and sows induced to farrow prematurely (Gustafsson *et al.* 1976; Wettemann *et al.* 1977). Ash and Heap (1973), Diehl *et al.* (1974) and Hendricks and Handlin (1974) suggest that PG administration caused luteal regression, and thereby induced parturition. The injection of PG to progesterone-treated sows did not significantly alter the decline in progesterone levels (Fig. 2). This finding was not unexpected, since it has been shown that both in early (Spies *et al.* 1959) and late (Coggins *et al.* 1977) gestation, exogenous progesterone induced corpora lutea regression in sows. Therefore it is possible that the mechanism by which exogenous PG initiates farrowing in late pregnant sows is related primarily to its effects on the myomet ium and cervix (Karim and Rao 1975).

The hormonal signal for the initiation of lactation in a number of species is considered to be a precipitous fall in the concentration of progesterone in the plasma around the time of parturition (Hartmann *et al.* 1973; Kuhn 1977; Kulski *et al.* 1977). Studies in the sow (Martin *et al.* 1978) suggest that progesterone withdrawal acts as a trigger for the initiation of lactation. The similarity between the initiation of lactation in the three groups of sows (Fig. 2) substantiates this suggestion. Sherwood *et al.* (1978) denoted the onset of lactation as the time when milk could be readily expressed from the teats of the sow and concluded that progesterone treatment did not delay the onset of lactation. In contrast, milk could not be expressed until the day of farrowing in the present study. The reason for this difference is unclear. However, it is possible that the stress of repeated vena cava puncture in late pregnancy (Sherwood *et al.* 1978) elevated blood cortisol which in turn may have influenced the initiation of lactation (see Denamur 1971). The maintenance of lactation assessed by piglet growth rate was not affected by the administration of progesterone to the sows in late pregnancy (Table 1).

The control of farrowing time has important practical applications for commercial piggeries. The present investigation demonstrates that a combination of both the delay and induction of farrowing with progesterone and PG respectively, provides a greater control over farrowing than that achieved by PG alone.

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