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Effects of placental pathology on maternal plasma progestagen and mammary secretion calcium concentrations and on neonatal adrenocortical function in the horse

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Summary. Between 1985 and 1990, 25 Thoroughbred mares were classified as having an abnormal pregnancy on the basis of precocious signs of impending parturition. Throughout the remainder of their pregnancies, plasma progestagen and mammary secretion calcium concentrations were monitored. After parturition, evidence of placental pathology was recorded and their foals were assessed with regard to adrenocortical function and behaviour. Seven pony mares were used to establish a model of placental pathology and, following induced placental separation, were subjected to the same protocol. Control animals consisted of 35 Thoroughbred mares and 39 pony mares, all considered to have normal pregnancies. Of the 25 abnormal mares, 16 had precociously increased plasma progestagen concentrations, 17 had precociously increased mammary calcium concentrations and 24 had an abnormal placenta. Eighteen live foals resulted, of which 11 appeared abnormal on the basis of behaviour. Adrenocortical function was assessed in 13; 4 had normo- and 3 hypo-function and 6 were intermediate. These results were independent of gestational age at delivery. Of 13 foals examined for plasma progestagens, 7 had normal and 6 abnormal concentrations. Following placental separation in the pony mares, maternal plasma progestagen concentrations increased in 4 of the 7 mares within 4–11 days and in 1 after 42 days; there was placental pathology in 3 of these mares, 1 of which aborted at 287 days gestation. There was no increment in progestagens in the remaining 2 mares, which aborted at 240 days and 271 days. It was concluded that placental dysfunction may be diagnosed from early plasma progestagen increments prior to 308 days gestation; and that foals that survive birth in these circumstances may be physiologically immature but often have normal or intermediate adrenocortical function, irrespective of gestational age. This is in contrast to foals born prematurely without maternal plasma progestagen or mammary secretion calcium increments.

Introduction

Endocrine changes that prepare mare and fetus for delivery are numerous and complex (Pashen, 1984; Silver & Fowden, 1988). Two of the most studied and easily identifiable changes are the increase in several metabolites of progesterone (progestagens) in maternal plasma during the last few weeks before delivery (Barnes *et al.*, 1975; Burns & Fleeger, 1975; Ganjam *et al.*, 1975; Lovell *et al.*, 1975); and the enlargement of the mammary glands with asssociated increase in mammary secretion, calcium and potassium concentrations (Peaker *et al.*, 1979; Ousey *et al.*, 1984). Holtan *et al.* (1975; 1991) identified the predominant progestagens as being 5α-pregnane-

3,20-dione (5α-DHP), 5α-pregnane-3β,20α-diol (βα-diol) and 20α-hydroxy-5α-pregnan-3-one (20α-5P), which all increase substantially during the last few weeks of pregnancy.

In mares delivering prematurely (i.e. before about 320 days gestation) similar changes may occur. For example, mares carrying a twin pregnancy may have mammary development and 'run milk' from about 225 days gestation prior to abortion or delivery of a live fetus days, weeks or months subsequent to the initiation of these changes. The same pattern occurs in singleton pregnancies often in association with placental pathology. The association between placental pathology and precocious onset of lactation and increase in maternal plasma progestagen concentration has not previously been studied systematically.

Foals resulting from induced or spontaneous birth, before increments in mammary secretion calcium concentrations occur, suffer hypo-adrenocortical function (Rossdale and Silver, 1982; Silver *et al.*, 1984; Ousey *et al.*, 1984). However, foals delivered prematurely following pre-parturient increments in maternal plasma progestagens and mammary secretion calcium concentrations frequently have normal adrenocortical function (Rossdale and Silver 1982). The adrenal cortex, known to play a central role in the 'switching on' mechanisms for birth in the ovine and porcine fetus may also be important in the equine fetus. A paradoxical increase in plasma progestagen concentrations during the first 4 days post partum has been observed in maladjusted individuals resulting from disturbed pregnancies (P. D. Rossdale, unpublished data). These increments have been shown to consist mainly of pregnenolone and pregnendiol (Houghton *et al.*, 1991). It has been hypothesized that the increments may be due to disturbances in adrenocortical function, to hepatic/metabolic derangement or disturbed renal clearance.

The aims of this study were: (1) To test the hypothesis that early increments in maternal plasma progestagen and/or mammary secretion calcium concentrations can be used as an indicator of placental pathology. (2) To investigate the pathophysiology of foals resulting from such pregnancies, with particular reference to adrenocortical function, behaviour and increased plasma progestagen concentrations. (3) To support observations made on field cases, using an experimental model of placental pathology.

Materials and Methods

Animals

Clinical cases. Twenty-five Thoroughbred mares encountered in practice between 1985 and 1989 were selected because they presented with signs of premature pregnancy termination (e.g. mammary development, vaginal discharge).

Experimental animals. Seven pony mares, selected at random from a herd with known mating dates, were subjected to induced placental separation to create an experimental model of placental pathology.

Foals. Foals from the clinical cases and experimental pony mares were used to assess the effect of abnormal pregnancies.

Controls. These consisted of 35 Thoroughbred mares and 39 pony mares (from the same herd as the experimental animals) considered normal on the basis of gestational age at foaling, signs of impending parturition occurring no more than 2 weeks prior to delivery, a placenta with no gross appearance of pathology and a foal with normal adaptive behaviour patterns and absence of clinical signs. Because data were not available for many of the foals delivered by control mares, blood samples were collected from a further 75 normal foals (42 Thoroughbreds and 33 ponies) to establish baseline data for plasma progestagen concentrations.

Protocols

Clinical cases. Observations on the 25 Thoroughbred mares were initiated as soon as signs of impending parturition were apparent. Sequential blood samples and mammary secretions were drawn at 1- to 4-day intervals up to spontaneous parturition, for measurement of plasma progestagen and calcium concentrations, respectively. No

hormonal treatment was administered to any mare. A small number received anti-mycotic drugs if fungi were recovered from vaginal discharge and some mares received intramuscular (i.m.) procaine penicillin (6000 mg/day for 4 days; Intervet, Cambridge, U.K.).

Experimental animals. Experimental procedures on the 7 pony mares were performed between 228 and 267 days gestation. These consisted of sedation with intravenous (i.v.) detomidine hydrochloride (5 mg Domosedan; Farmos); then antiseptic washing and preparation of the perineum followed by the introduction of a videoendoscope (Welch Allyn, Seward Medical Ltd, London) sterilised in disinfectant (Sporocyclin; Seward Medical) and rinsed in sterile distilled water immediately prior to insertion. When the cervix was located visually, it was expanded with the forefinger and the end of the videoendoscope introduced into the uterus. Air was insufflated until separation of the placenta was visible. Air was then sucked out and the instrument withdrawn. The mares received procaine pencillin (6000 mg) i.m. once daily for 4 days and flunixin meglumine (500 mg) i.m. at the time of and 1 day following the procedure.

Blood samples were collected from the mares for at least 8 days prior to placental separation in order to establish a baseline for plasma progestagen concentrations; subsequently, collections were twice daily for 3 days and daily thereafter until delivery. During this period, mammary development and clinical signs, with particular reference to vaginal discharge, were noted.

Three mares were induced, at full term, using 5 i.u. oxytocin i.v. (Intervet). Another mare (No. 6) was induced by administration of 10 i.u. i.v. oxytocin at 271 days gestation because echographical observation had established fetal death. The remaining 3 mares foaled spontaneously.

Foals. In foals from clinical cases and experimental pony mares, blood samples were taken at 1, 2, 6, 12, 24, 36 and 48 h *post partum* and then daily until one week of age. The sample obtained at 2 h was used to measure the neutrophil:lymphocyte ratio as an indicator of adrenocortical function (see below). This was confirmed by an ACTH stimulation test (0·125 mg short acting Synacthen i.m., Ciba Geigy).

Controls. Blood samples were taken weekly from all control mares from approximately 200 to 305 days gestation. Thereafter, daily samples were obtained until spontaneous parturition. Mammary secretion calcium concentrations were measured from the onset of mammary development. Blood samples for plasma progestagen measurement were obtained from the 75 normal foals at the same intervals as for clinical and experimental foals.

Assessment of placental pathology

Pathology of the placenta was defined on the basis of gross examinations showing one or more of the following features: a large avillous area at any site, thickened cervical pole, necrotic areas where the villi were liquified or twin placentation.

Assessment of adrenocortical function

Adrenocortical function was evaluated according to Rossdale *et al.*, (1984) as (a) normal if the neutrophil:lymphocyte ratio was 2 or more within 3 h of birth and/or if the ACTH stimulation test was positive; (b) subnormal (hypofunction) if the neutrophil:lymphocyte ratio was 1·9 or less during the first 12 h post partum and/or if the ACTH stimulation test was negative; (c) Intermediate if the neutrophil:lymphocyte ratio was 1·9 or less at the first examination but increased to 2 or more within a further 12 h.

Assessment of behaviour

Periods taken to stand and suck were recorded. Foals were considered abnormal if they did not stand within 165 mins (Thoroughbreds) or 90 mins (ponies) and suck by 420 mins (Thoroughbreds) or 180 mins (ponies) (Rossdale, 1967; J.C. Ousey, unpublished data).

Analytical procedures

Progestagen concentrations were measured using a radioimmunoassay as described by Michel *et al.* (1986). In view of the substantial quantities and range of metabolites present in maternal peripheral blood plasma during the later stages of pregnancy, it is important to take into account the sensitivity and cross reactions of the antibody employed. The antiserum cross-reacted with progesterone (100%), 11α-hydroxyprogesterone (76%), 5αDHP (6·2%), corticosterone (2·1%), 17α-hydroxyprogesterone (2·0%), 11-deoxycorticosterone (1·7%), 20α-dihydroprogesterone (0·98%), 11-deoxycortisol (0·4%), 5α-pregnen-3ß-ol-20-one (pregnenolone; 0·4%) and 5α-pregnan-3ß-ol-20-one (0·34%). All other compounds tested cross-reacted < 0·1%. Inter-assay and intra-assay coefficients of variation were 9·2 and 4·9% respectively. The manufacturer's information did not include cross-

reaction with 5α-pregnen-3ß,20ß-diol (pregnendiol) or 20α-5P, but our own tests showed these to be 0·03% and 0·06%, respectively.

Mammary secretion calcium concentrations were measured using a Hitachi 705 automatic biochemistry analyzer and leucocyte counts performed on either a Coulter S880 semi-automatic haematology analyzer (1985-1989) or a Technicon H1 automatic haematology analyzer (1989–1990).

Results

Outcome of pregnancies

Clinical cases. Of the foals from abnormal pregnancies, 18 were singletons (14 live and 4 dead) and there were 7 sets of twins (4 live and 10 dead). Eight (57%) of the live singleton foals and 3 (75%) of the live twins survived without subsequent complication. The remaining 6 singletons and 1 twin were killed on humane grounds or died before one month of age. The mean ± s.d. gestational age at which these abnormal pregnancies terminated was 307 ± 33·8 days.

Experimental animals. Of the 7 pony mares, following placental separation, 4 delivered live foals; in 1 of these (No 1) delivery was unattended and therefore no data were available for the foal. The mean ± s.d. gestational age at parturition was 299 ± 33·6 days.

Controls. The 35 Thoroughbred and 39 pony mares all produced live foals at a mean ± 1 s.d. gestational age of 341 ± 7·3 days and 333 ± 12·5 days respectively.

Plasma progestagens

Controls. Mean ± 2 s.d. plasma progestagen concentrations measured in normal Thoroughbred (35) and pony (39) mares from approximately 200 days gestation to full term are shown in Figures 1a & 1b, respectively. Before 305 days gestation, values were grouped in weekly means and subsequently as daily means.

A normal progestagen profile in Thoroughbred mares was characterized by concentrations of < 10 ng/ml before about 310 days gestation and a pre-partum increase reaching an average value of about 25 ng/ml. The mean ± 2 s.d. gestational age at which plasma progestagens increased consistently above 10 ng/ml was 323 ± 15·3 days. Therefore, 308 days (i.e. 323 minus 15) was selected as the gestational age before which an increment in plasma progestagens was considered abnormal. Ten (3·5%) of the 284 samples collected from these normal mares had plasma progestagen concentrations above 10 ng/ml before this gestational age. This deviation would be expected for a normal population distribution where 2·5% (n = 7) of the samples lie outside the range of mean ± 2 s.d. The samples came from 5 mares; the increment was recorded on 1 occasion only in 3 of the mares, 2 occasions in 1 mare and 4 occasions in the remaining mare. Therefore, increments before 308 days should be considered abnormal only if they are consistent over 4 or more samples.

In control pony mares, the range of progestagen values before 300 days gestation was much greater and some indivduals consistently had values above 10 ng/ml (Fig 1b). Therefore, a classification of abnormality for the experimental animals was based on the sample before 308 days gestation where values were outside the 2 s.d. of the mean established for each individual prior to placental separation.

Plasma progestagen concentrations in the control foals over the first 168 h post partum are shown in Fig. 2. Values greater than 2 s.d. above mean concentrations after the first day were regarded as abnormal.

Clinical cases. Plasma progestagen concentrations were abnormal in 16 mares; 4 could not be

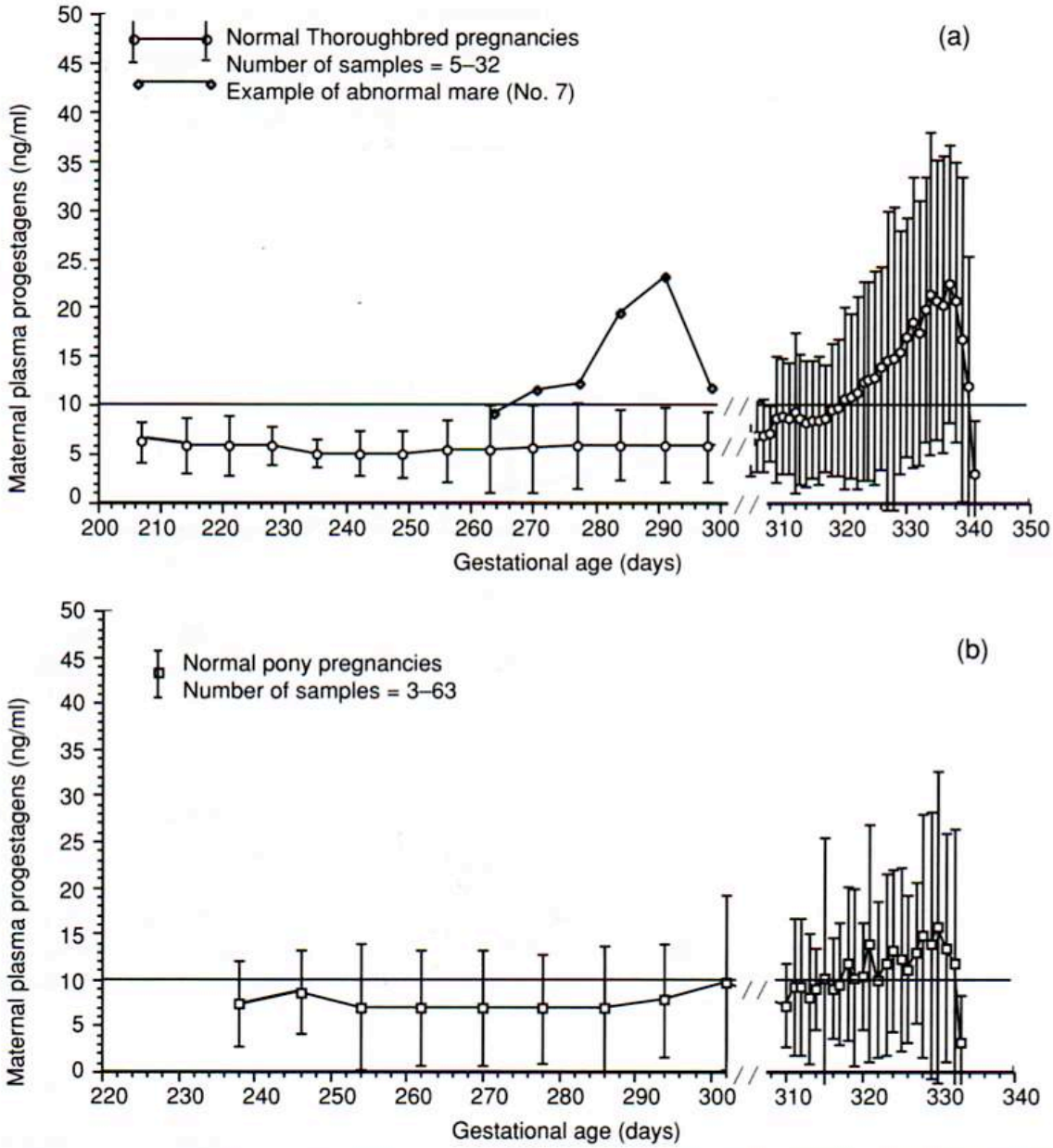

Fig. 1. (a) Mean ± 2 s.d. plasma progestagens in 25 normal Thoroughbred pregnancies from 200 days gestation to parturition (mean = 341 days) and an example of an abnormal pregnancy (No. 7). (b) Mean ± 2 s.d. plasma progestagens in 39 normal pony pregnancies from 230 days gestation to parturition (mean = 333 days). Values were grouped as weekly means up to 305 days gestation, and daily means after 305 days gestation.

considered under our criteria for normality (No. 25 aborted before Day 200 and Nos. 2, 3 and 9 presented after Day 308); and data were unavailable in a further 5 (Table 1). Figure 1a includes data for one animal (No. 7) that was typical of the plasma progestagen profile for clinical cases. The mean ± s.d. gestational age at first presentation of the 16 cases was 264 ± 34·0 days.

Experimental pony mares. The results from 7 mares subjected to placental separation between Days 228 and 267 days gestation are shown in Table 2. Plasma progestagen concentrations increased before 308 days gestation to above 2 s.d. from the pre-operation mean in 5 of the 7 individuals. This increase occurred between 4 and 42 days after placental separation. In the

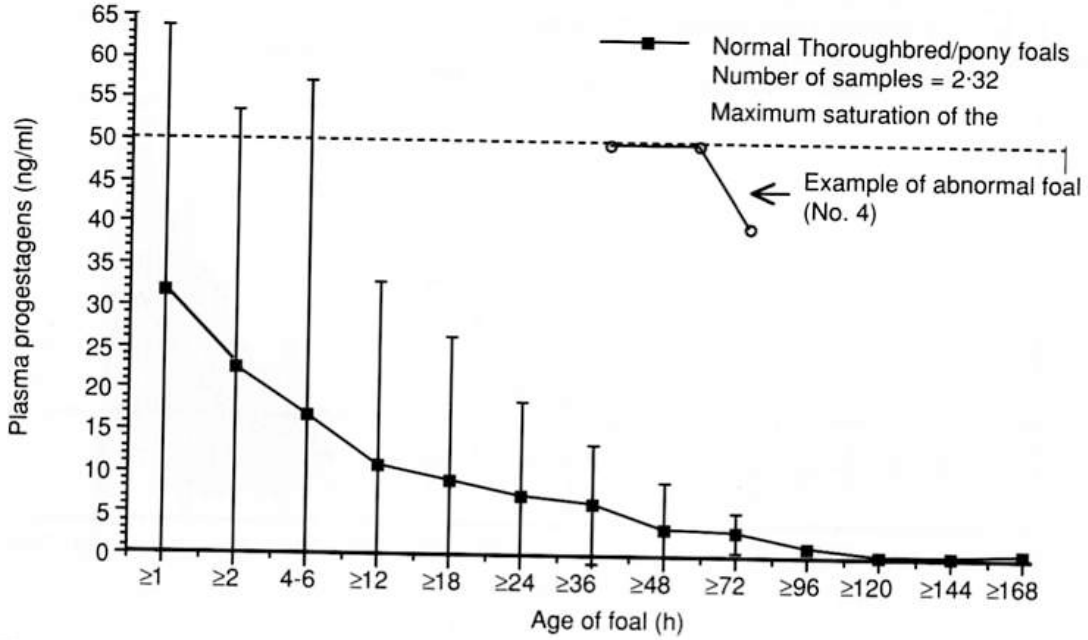

Fig. 2. Mean ± 2 s.d. plasma progestagen concentrations in 75 normal foals (—■—; number of samples 2–32) (Thoroughbred n = 42, pony n = 33) from birth to age 168 h and an example from an abnormal foal (No. 4).

remaining 2 individuals (Nos. 2 and 6), pregnancy terminated between 9 and 16 days after placental separation without an increase in plasma progestagen concentrations.

Foals. Plasma progestagen concentrations measured in foals from clinical cases between 2 and 7 days post partum were normal in 7 foals, elevated in 6 and data were unavailable in 5 (Table 1).

Of the 4 live foals from experimental pony mares, 2 had abnormal and 1 normal plasma progestagen concentrations (Table 2) and data were unavailable for 1 foal.

Mammary secretion calcium concentrations

Controls. Mean ± 2 s.d. calcium concentrations in mammary secretions, according to gestational age, are shown for Thoroughbred (n = 35) and pony (n = 39) mares in Figs. 3a and b. In both breeds, an increase in calcium concentrations above 10 mmol/litre occurred no earlier than 9 days before parturition, reaching maximum values on the day of foaling.

Normal gestational length in mares is 320–360 days; therefore, on the basis of these data, an elevation in mammary secretion calcium concentrations above 10 mmol/litre before 311 days gestation (i.e. 320 minus 9 days) was defined as abnormal for Thoroughbred and pony mares.

Clinical cases. Mammary secretion calcium concentrations were increased prematurely in 17 cases and the mean ± s.d. gestational age at which this occurred was 283 ± 18·8 days (Table 1). Four mares (Nos. 3, 9, 12 and 13) had normal calcium concentrations but could not be considered under our criteria of abnormality because the gestational age at which each case presented was above 311 days. In the remaining 4 mares, data were unavailable in 2, whereas 2 mares (Nos. 21 and 25) had no mammary secretions pre-partum and aborted twins.

Figure 3a includes data for 1 mare (No. 1) that were typical of mammary secretion profiles for the clinical cases.

Table 1. Classification of abnormalities in 25 Thoroughbred mares and their foals

	Maternal criteria						Foal	Foal criteria			
No.	1	1a	2	2a	GA at birth	Placental pathology	at birth	3	4	5	Outcome
1	+	290	+	290	305	+ avillous, fungus	D				
2	-		+	309	324	+ partly avillous	L	-	-	-	Lived
3	-		-		354	+	L	-	u	u	Lived
4	u		+	293	301	+ avillous, oedema at pole	L	+	-	+	Euthanasia age 70 h. *E. coli* infection.
5	+	272	+	271	276	+ edema, fungus	D				
6	+	249	+	249	277	+ avillous, oedema	D				
7	+	266	+	286	299	+ avillous, oedema at pole	L	+	±	-	Euthanasia age 90 h.
8	+	291	+	302	313	+ avillous, oedema at pole	L	+	±	+	Lived
9	-		-		343	+ avillous body	D				Died at delivery. Blood filled thoracic cavity.
10	+	285	+	292	305	+ oedema, necrotic	L	+	±	-	Euthanasia age 1 month -incomplete ossification of carpal bones.
11	+	296	+	303	334	-	L	+	+	+	Lived.
12	u		-		317	+ avillous, oedema	L	+	u	u	Euthanasia age 1 h.
13	+	295	-		339	+ avillous	L	-	±	u	Lived.
14	+	270	+	271	294	+ oedema pole	L	+	+	u	Euthanasia age 0·5 h.
15	+	281	+	281	301	+ avillous	L	+	-	+	Lived.
16	+	255	+	254	346	+ avillous	L	-	-	+	Lived.
17	+		+	9·299	330	+ thin, oedematous	L	-	u	-	Lived.
18	u		u		314	+	L	+	±	u	Died age 28 h. *Staph. aureus/E.coli.*
19	+	191	+	258	282	+ twin	2 × D				Pre-viable twins.
20	+	197	+	266	267	+ twin	2 × D				Pre-viable twins.
21	+	223	-		285	+ twin	2 × D				Pre-viable twins.
22	u		u		340	+ twin	L	+	u	-	Smaller twin - survived
							L	-	u	-	Larger twin - survived
23	+	271	+	287	302	+ twin	1 × L	+	+	+	Larger twin. Euthanasia age 47 h.
							1 × D				Smaller twin. Autolysed.
24	u		+	305	338	+ twin	1 × L	-	±	-	Larger twin. Lived.
							1 × D				Smaller twin. Mummified.
25	-		-		194	+ twin	2 × D				Pre-viable twins.

Maternal criteria: (1) plasma progestagens; (1a) gestational age at which abnormal progestagen concentrations first detected; (2) mammary secretion calcium; (2a) gestational age at which abnormal calcium concentrations first detected. Symbols: + = abnormal (or hypoadrenal function); - = normal (or normoadrenal function); ± = intermediate adrenal function; u = data unavailable; GA = gestational age; L = live foal; D = dead foal. Foal criteria: 3 = behaviour; 4 = adrenocortical function; 5 = plasma progestagens.

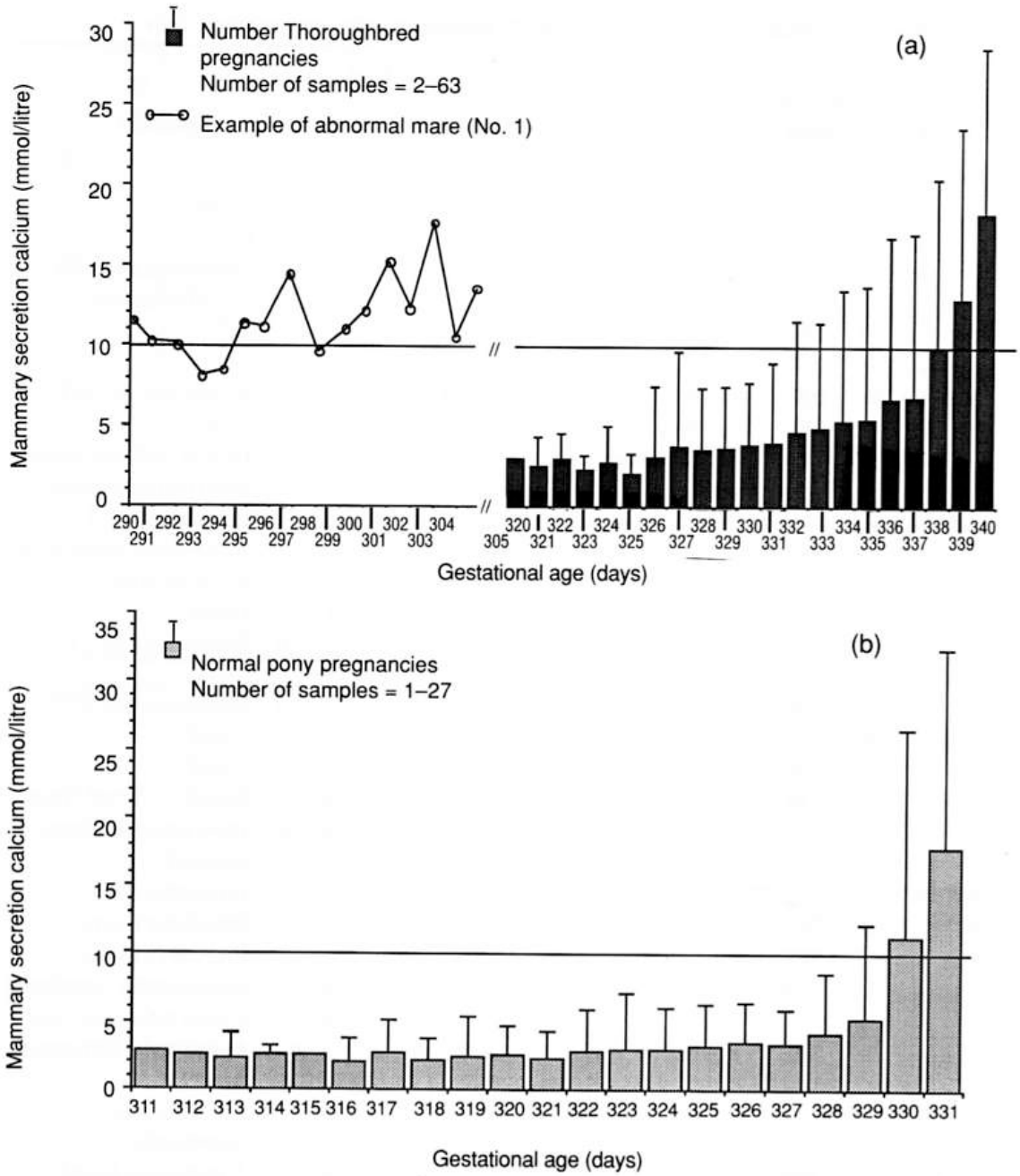

Fig. 3. (a) Mean ± 2 s.d. calcium concentrations in pre-partum mammary secretions from 35 normal Thoroughbred pregnancies and an example of an abnormal pregnancy (No. 1). (b) Mean ± 2 s.d. calcium concentrations in pre-partum mammary secretions from 27 normal pony pregnancies.

Experimental animals. Mammary secretion calcium concentrations did not increase pre-term in any of the 4 individuals from which samples were obtained (Table 2).

Adrenocortical function

Controls. Foals from the control Thoroughbred and pony mares all had normal adrenocortical function.

Table 2: Classification of abnormalities in 7 experimental pony mares and their foals

No.	GA at PS	Maternal criteria 1	1a	2	Placental pathology	PS to birth (days)	GA at birth	Delivery	Foal at birth	Foal criteria 3	4	5	Outcome
1	249	+	4	u	u	75	324	Spont.	L	u	u	u	Lived
2	228	-		u	u	9-16	237-244	Spont.	D				No information
3	267	+	11	-	+ oedema, necrotic	50	317	Induced	L	+	±	+	Lived
4	264	+	7	-	- normal	59	323	Induced	L	-	±	-	Lived
5	259	+	4	u	+ oedema, avillous	28	287	Spont.	D				Died at birth before delivery
6	262	-		-	+ oedema, avillous	9	271	Induced	D				Died 3·5–7·5 h before delivery
7	262	+	42	-	+ avillous pole	66	328	Induced	L	-	±	+	Lived

Maternal criteria: (1) plasma progestagens; (1a) time (days) from placental separation to first increase in plasma progestagens; (2) mammary secretion calcium. Foal criteria: 3 = behaviour; 4 = adrenocortical function; 5 = plasma progestagens. Symbols: - = normal; + = abnormal; ± = intermediate adrenocortical function; u = data unavailable; GA = gestational age; PS = placental separation; Spont. = spontaneous; L = live; D = Dead.

Foals. Of the foals from clinical cases for which data were available (Table 1), 4 had normal, 6 intermediate and 3 hypo-adrenocortical function.

Of the 4 live foals from experimental pony mares, 3 had intermediate adrenocortical function and data are unavailable for 1 (Table 2).

Behaviour

Controls. The foals from control mares were assessed as having normal behaviour according to the criteria used.

Foals. Of the 18 live foals from clinical cases, behaviour was considered normal in 7 and abnormal in 11 (Table 1). Of the 4 live foals from experimental pony mares, two exhibited normal behaviour, one was abnormal and one was not classified (Table 2).

Placental pathology

Controls. Placental pathology was not observed in any of the control mares.

Clinical cases. Placental pathology was present in 24 of the 25 abnormal pregnancies. Details are given in Table 1.

Experimental animals. Pathology of the placenta was present in 4 of the 5 placentae available for examination following delivery. Details are provided in Table 2.

Discussion

This work has confirmed previous reports of increasing plasma progestagen concentrations in maternal blood during preparation for parturition (Barnes *et al.*, 1975; Burns and Fleeger, 1975; Ganjam *et al.*, 1975; Lovell *et al.*, 1975). It has extended these previous findings by identifying the mean gestational age at which pre-parturient increments normally occur in Thoroughbreds and ponies and has shown the greater variability in concentrations during the last third of pregnancy in ponies compared with Thoroughbreds. Pony mares appear to fall in 1 of 3 groups, those with concentrations less than 5 ng/ml with a late increment occurring within 3 or 4 days of parturition, those with patterns similar to Thoroughbreds and those with higher pre-partum concentrations (about 10 ng/ml), which exhibit varying patterns of increase prior to foaling. Whether these variations are quantitative or qualitative has not been established but care has to be taken to establish the exact cross-reactions of antibody used in RIA for this purpose. Our antibody cross-reacted 6·2 per cent with 5α-DHP, 0·06% with βα-diol and 0·06 per cent with 20α-5P, all of which increase markedly within 20 days of parturition (Holtan *et al.*, 1991).

We have shown that placental pathology is strongly correlated with increments in maternal plasma progestagens prior to 308 days gestation. In 4 of 5 cases where placental pathology occurred in the absence of a premature increment, the individual presented later than 308 days. Our findings extend the observation of van Niekerk and Morgenthal (1982), who employed an antibody in their assay showing significant cross reactivity with 5α-DHP. However, these authors reported a depressive effect on plasma progestagen by a variety of stimuli including pain, infectious disease and 'emotional disturbances'.

Measurements of maternal plasma progestagens and mammary secretion calcium electrolytes have been used to predict the development of fetal readiness for birth (Ousey *et al.*, 1984) and the current work indicates that these 2 parameters are useful in the diagnosis of abnormal pregnancies, provided measurements are made before about 310 days gestation.

We have shown that abnormal pregnancies involving placental pathology often result in foals that suffer premature-like signs at whatever gestational age they are delivered. However, irrespective of gestational age at delivery, abnormal pregnancy appears to involve some degree of maturation of the pituitary adrenocortical axis as evidenced by the low proportion (3/13) of foals with hypoadrenocortical function.

Plasma progestagen concentrations in the newborn foal are high at birth (Short, 1959). Ganjam *et al* (1975) reported that concentrations were decreasing by the end of the first day post partum. Our study confirms this and, by age 2 days, concentrations had fallen to near zero. Our findings that sick foals, especially those that are dysmature, have elevated plasma concentrations on the second and subsequent days post partum appears to be an original observation not previously reported in the literature. The particular progestagens involved have subsequently been identified as being predominantly pregnenolone and pregnendiol (Houghton *et al.*, 1991) of which pregnenolone is a precursor for the 17α-hydroxyprogesterone pathway through to cortisol. It is possible that these changes in progestagens may reflect abnormalities of this glucocorticoid pathway in the adrenal cortex. Alternatively, it may reflect abnormal hepatic steroid metabolism or failure in renal clearance mechanisms. Plasma concentrations, measured by our RIA antibody, increased rather than decreased following birth in maladjusted foals and eventually decreased to near zero concentrations during the phase of recovery, sometimes several days post partum. In foals that do not survive, the concentrations may remain elevated until death.

Results from the 4 surviving twins were similar to the singleton pregnancies in terms of

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