Endocrine changes and luteal morphology during pregnancy in muskoxen (*Ovibos moschatus*)

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Progesterone, oestradiol and oestrone were measured in plasma from four captive muskoxen during three consecutive pregnancies (1983–1984, 1984–1985 and 1985–1986). Jugular blood samples were collected weekly (1983) or on an alternating 3:4 day schedule (1984–1986) during the first 12–15 weeks and last 6–10 weeks of pregnancy. Sampling during mid-pregnancy was at intervals of 2 weeks (1983 and 1985) or 1 week (1986). Duration of gestation was about 34 weeks (235 ± 4 (SD) days ($n = 10$), range 230–242 days). Progesterone remained at concentrations similar to those found during the luteal phase of the oestrous cycle for the first 10–12 weeks (mean $\pm$ SEM 1.6 ± 0.1 ng ml⁻¹) after which it rose to a peak (mean 5.5 ± 0.65 ng ml⁻¹) between weeks 12 and 20. In all ten pregnancies progesterone concentrations declined dramatically between weeks 20 and 22 to luteal phase values where they remained until parturition. The decline was accompanied by an increase in oestradiol and oestrone concentrations which reached mean peak values of 199.23 ± 87.23 pg ml⁻¹ and 980.48 ± 203.91 pg ml⁻¹, respectively. Corpora lutea collected from wild muskoxen between 45 and 80 days gestation all showed histological evidence of regression, while corpora lutea from mid-gestation (112–125 days) were in advanced stages of involution. Repeated ovarian ultrasonography of captive muskoxen during the first 100 days of pregnancy confirmed these findings. The unusual, early regression of the corpus luteum of pregnancy indicates that progesterone and oestrogen of mid- and late pregnancy are probably of placental origin. The temporal relationship between the concentrations of these hormones during late pregnancy differs from those of domestic species and is apparently unique among ruminants.

Introduction

Similarities in reproductive endocrinology and anatomy are among the many common features shared by muskoxen, sheep and goats, all members of the subfamily, Caprinae (Simpson, 1945). The uterus, ovaries and placenta of the muskox closely resemble those of sheep and goats (Rowell *et al.*, 1987) as do duration of oestrous cycles and endocrine changes during the oestrous cycle (Rowell and Flood, 1988). One notable difference between muskoxen and goats and sheep is the lack of a grossly visible corpus luteum in muskox ovaries 3–6 weeks before parturition. At this late stage of pregnancy only a small scar can be detected histologically (Rowell *et al.*, 1987).

There is a major difference between goats and sheep in the source of progesterone during pregnancy (Flint *et al.*, 1983). Goats depend on luteal progesterone throughout gestation (Meites *et al.*, 1951), whereas sheep require luteal progesterone only for the first 50–60 days of pregnancy (Casida and Warwick, 1945). Muskoxen are therefore similar to sheep in

their ability to support a fetus during the later stages of gestation in the absence of a corpus luteum. However, complete disappearance of the corpus luteum in the muskox makes this species most unusual and suggests that its endocrine control of pregnancy differs from that of sheep.

Existing reports of peripheral progesterone concentrations in pregnant muskoxen are all derived from single samples taken from captive muskoxen in Norway, as a means of pregnancy detection (Nilssen *et al.*, 1984) or from wild muskoxen in the Canadian Arctic immediately after death (Rowell, 1980; Tessaro *et al.*, 1984). The purpose of this study was to describe the patterns of reproductive steroids in peripheral blood and the changes occurring in the corpus luteum during pregnancy in muskoxen.

Materials and Methods

Captive animals

Female muskoxen maintained at the University of Saskatchewan were used for endocrine and morphological studies between

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1983 and 1989. The cows were 1.5 years old at the beginning of the study and were kept together in outdoor pens with non-pregnant females, bulls and castrates. They were fed supplemented oat pellets and had free access to brome-alfalfa hay and water. The muskoxen had been bottle raised and were fully accustomed to handling and restraint so that twice weekly jugular venepuncture or transrectal ultrasonography caused minimal observable stress (Rowell, 1991).

Sample collection

Four pregnant females were sampled by jugular venepuncture throughout their first pregnancy and three of the four cows were sampled during their next two pregnancies. During early and late pregnancy samples were taken once (1983) or twice (1984, 1985) a week. Bimonthly (1983) or weekly (1984, 1985) samples were collected during mid-pregnancy. The ten pregnancies included in this study were all carried to term.

Cows were observed for signs of oestrus and mating (Rowell and Flood, 1988) and the day of mating was designated as day 0. Over the three breeding seasons the earliest fertile mating occurred on 24 September and the latest on 15 November. The endocrine data for all pregnancies have been normalized to day 0.

The samples (approximately 10 ml) were collected between 09:00 and 12:00 h in heparinized evacuated tubes (Vacutainer: Becton-Dickinson, Rutherford, NJ), refrigerated immediately and centrifuged at 1200 g for 10 min within 1 h of collection to optimize progesterone preservation (Rowell and Flood, 1987). Plasma was stored at -22°C until assayed.

Assays

Progesterone concentrations were determined in duplicate samples using a double antibody method and ^{125}I -labelled progesterone (Rawlings *et al.*, 1984; Rowell and Flood, 1988). Coefficients of variation were calculated from a high (about 2.5 ng ml^{-1}) and a low (about 1.3 ng ml^{-1}) reference pool of sheep plasma. The mean intra-assay coefficients of variation were 7.4 and 9.8% for high and low references, respectively. The interassay coefficient of variation was 11.7 (high) and 14.6% (low).

Oestradiol, from six of the ten pregnancies, was measured in 0.5 ml aliquots of muskox plasma extracted in ethyl ether and assayed using [^3H]oestradiol (Joseph *et al.*, 1992). Standards were extracted from charcoal-stripped serum (CSS) from castrate muskox, eliminating the need for an extraction calculation. The blank, also CSS, was below assay sensitivity. The range of the standard curve was 0.5–200 pg and the sensitivity was 1 pg ml^{-1} . Intra-assay coefficients of variation, determined from low (2 pg) and high (10 pg) references were 6.8 and 8.2%, respectively, whereas interassay coefficients of variation were 16.7 (low) and 5.2% (high).

Oestrone from three of the ten pregnancies was similarly assayed using [^3H]oestrone: standards and 1 ml aliquots of muskox plasma were extracted with ethyl ether from CSS. The antiserum (raised in sheep against 1,3,5,10-oestratriene-3-ol-6,17-dione-6-carboxy-methylxime: BSA, (Steraloids E2056; Wilton, New Hampshire) had the following crossreactions: oestradiol, 0.4% and 17 α -oestradiol, 0.3%; oestriol, cortisol,

cholesterol, cortisone, corticosterone, testosterone, dihydro-testosterone, androstene-3,17-dione, progesterone and pregnenolone all crossreacted $<0.01\%$. The blank, also CSS, did not differ from zero. The standard curve was from 10 to 500 pg ml^{-1} and assay sensitivity was 5 pg ml^{-1} . The intra-assay coefficients of variation for a high (about 50 pg ml^{-1}) and a low (about 20 pg ml^{-1}) concentration reference ewe plasma were 10.1 and 8.4% and interassay coefficients of variation were 7.5 and 12.8%, respectively.

Histology of ovaries from pregnant, wild muskoxen

Ovaries were collected during muskox harvests on Banks Island on 11–13 December 1985 ($n = 19$), 4 November 1987 ($n = 11$) and 22–23 September 1988 ($n = 12$). The ovaries were bisected longitudinally and fixed in 10% buffered formalin. After fixation, measurements of macroscopically visible corpora lutea were made by taking two diameters at right angles. Fetal weights, fetal transcranial diameter (measured just behind the orbits with callipers) or crown–rump lengths (embryos) were used to estimate the stage of gestation. Ovaries collected in December 1985 were not accompanied by a fetus from the same pregnant female and the approximate stage of gestation could only be inferred by comparison with weights of 13 fetuses collected from other females on the same occasion. Fetal age was estimated using the formula of Huggett and Widdas (1951), comparison with cattle and sheep fetal development and crown–rump measurements (Evans and Sack, 1973), and a comparison of transcranial measurements with those collected by ultrasonography from captive muskoxen (Pharr and Rowell, 1989).

After fixation, ovaries were embedded in paraffin wax, sectioned at 5–6 μm and stained with haematoxylin and eosin or Gomori's trichrome stain. The ovaries were not serially sectioned and no measurements or volumes were calculated from sectioned tissues.

Transrectal ultrasonography

The genital tracts of four tame muskoxen were examined at regular intervals by ultrasonography in three successive breeding seasons (1988, 1989, 1990). The animals were lightly sedated with 60 mg acepromazine (Atravet Granules, Ayerst) given orally 30–45 min before examination, and restrained in a headgate immediately before scanning. In 1988, examinations were performed weekly from about day 50 of gestation until the corpus luteum could no longer be detected. In 1989, the same animals were examined at intervals of 14 days from the time of conception until the corpus luteum could no longer be identified. In 1990, additional data were collected during very early pregnancy.

Scans were performed with a Tokyo Keiki LS-200 instrument equipped with a 5 MHz intrarectal transducer (Products Group International, Boulder, CO) (1988, 1989) or an Aloka DS-210 instrument with a 7.5 MHz intrarectal transducer (1990). Upon insertion of the probe into the rectum, the cervix was located and the transducer moved along the dorsal surface of the reproductive tract to facilitate orientation. The uterine horns were examined in longitudinal and oblique planes; the transducer was

then directed laterally to examine the ovaries. The conceptus (Kastelic *et al.*, 1988) and the ovaries (Pierson *et al.*, 1988) were evaluated as described previously in cattle. When a corpus luteum was identified, the image was frozen when the luteal dimensions appeared maximal. The greatest linear dimension and the greatest dimension perpendicular to it were recorded. Luteal volumes were calculated on the assumption that the corpus luteum was approximately ellipsoidal (volume = $\frac{4}{3}\pi abc$ where a , b and c are the radii) and that the unknown axis was the mean of the measured axes.

Results

Duration of gestation was 235 ± 4 days (mean $\pm$ SD), range 230–242 days, an average of 34 weeks. Of the ten pregnancies, eight resulted in normal deliveries with healthy calves, one (presented caudally with flexed hocks) was delivered with assistance and one was a stillbirth. Examination of afterbirths from all pregnancies revealed placentitis in the intercotyledonary regions that ranged in severity from a trace ($\leq 1\%$ of tissue affected, $n = 3$) to mild (1–10% of tissue affected, $n = 5$) to moderate (10–50% of tissue affected, $n = 2$) (Blake and Rowell, 1989). The placentae from the caudal presentation and the stillbirth were the most severely affected.

Hormones

During the first 10–12 weeks of gestation plasma progesterone remained at peak luteal phase concentrations (mean $\pm$ SEM 1.6 ± 0.1 ng ml⁻¹). Progesterone concentrations began to rise between weeks 10–12 reaching peak concentrations (mean 5.5 ± 0.7 ng ml⁻¹) by weeks 16–20. In all ten pregnancies, progesterone concentrations declined dramatically between weeks 20 and 22 (mean 2.0 ± 0.8 ng ml⁻¹) (Fig. 1a, b). These concentrations were similar to those of early pregnancy and were maintained until just before parturition. A slight increase of 1–2 ng ml⁻¹ was evident in some individuals 2 weeks before parturition. In all animals the decline occurred at the same stage of gestation regardless of whether conception occurred in September or November.

Both oestradiol and oestrone remained low for the first 20 weeks. However, as progesterone concentrations declined, circulating concentrations of both oestrogens increased to peak values (mean 980 ± 203 pg ml⁻¹ for oestrone and a mean of 199 ± 87 pg ml⁻¹ for oestradiol). There were large fluctuations in the concentrations of both oestrogens during the last 5–6 weeks of pregnancy (Fig. 1a).

Morphology of the corpus luteum

On the basis of fetal development, tissues collected in September were estimated at 4–6 weeks; the November collection, 10–12 weeks and the December collection 16–18 weeks gestation.

Fixed corpora lutea from 4–6 weeks gestation were yellow in colour and almost circular in cross-section with gross, mean dimensions of 1.1 cm $\times$ 1.2 cm. Only four of twelve specimens had remnants of a 'crown' and caused an obvious swelling within the ovary (Fig. 2). Large luteal cells with round, vesicular

Fig. 1. (a) Plasma progesterone (■) (mean $\pm$ SEM, $n = 10$), oestradiol (▲) (mean $\pm$ SEM, $n = 6$) and oestrone (●) (mean $\pm$ SEM, $n = 3$) concentrations during pregnancy in captive muskoxen. The data were normalized to the day of mating but parturition dates differed. The last point on the progesterone curve (35 weeks) is a mean of *postpartum* samples from all pregnancies. (b) The pattern of progesterone concentrations in three representative, pregnant muskoxen. Although there were differences in individual values, the progesterone decline at 20 weeks was clearly evident in all cases. Blood sampling stopped 3–4 days before parturition. The times of parturition are indicated by the arrows.

nuclei and prominent nucleoli were the most obvious type of cell. The remainder of the tissue comprised small luteal cells, connective tissue and vascular elements. The corpora lutea had a connective tissue core with strands of connective tissue radiating into the parenchyma. Although the majority of the cells appeared healthy, cell death and intravascular cellular debris were evident (Fig. 3a, b). Lymphocytes, neutrophils and plasma cells were found throughout the tissue.

At 10–12 weeks gestation the corpora lutea were macroscopically smaller (0.82 cm $\times$ 0.99 cm) and none protruded from the surface of the ovary. Luteal size was variable and did not correlate well with estimated fetal age (Fig. 2). Connective tissue cores are evident on gross examination. Apparently healthy large luteal cells were still visible in all corpora lutea but the cells were less distinct. Marked eosinophilia of luteal cell cytoplasm, karyorrhexis and pyknosis were evident (Fig. 3c). Interstitial connective tissue had increased and pigment accumulation was apparent. Many capillaries contained cellular debris and thick walled vessels were numerous. Lymphocytic invasion from the periphery was noted in addition to clusters of lymphocytes within the corpus luteum. The cellular changes

Fig. 2. Drawings of representative sections of muskox ovaries at (a) 4–6, (b) 10–13, (c) 16–18 weeks gestation. The loss in size and definition of the corpus luteum is evident. Bar = 0.5 cm.

were patchy in some corpora lutea and pockets of apparently healthy tissue could be found indicating that degeneration had not occurred uniformly.

Only eight of 19 (42%) animals killed at 16–18 weeks gestation had a grossly visible corpus luteum on bisection of the ovaries (Fig. 2). Under light microscopy all corpora lutea stained intensely for connective tissue with Gomori's trichrome and neither large nor small luteal cells could be found (Fig. 3d).

Estimation of luteal volume by transrectal ultrasonography revealed that luteal regression was a gradual process that began during, or before, week 8 of pregnancy and was complete by week 15 (Fig. 4). Thus, regression started well before the sharp mid-pregnancy rise in peripheral progesterone concentration became evident.

Discussion

Pregnancy in the muskox has at least two unusual features. First, histological examination of ovaries from wild muskox cows

and repeated ovarian ultrasonography of tame muskoxen has shown that the corpus luteum of pregnancy shrinks steadily during early gestation and is reduced to a scar devoid of luteal cells by the sixteenth week of pregnancy. Second, at 20–22 weeks gestation, two thirds of the total gestation period, progesterone concentrations fall sharply from their mid-pregnancy maximum to concentrations similar to those seen during the luteal phase of the oestrous cycle (Rowell and Flood, 1988).

Complete regression of the corpus luteum during pregnancy is known to occur in horses (Squires *et al.*, 1974), but has not been reported in other species. Of the ruminants that have been studied in any detail, cattle, which produce both placental and luteal progesterone (Dobson and Kamonpatana, 1986), show little change in luteal volume during pregnancy, although the number of luteal cells is significantly reduced near term (Shemesh, 1990). Goats depend completely on a functional corpus luteum throughout pregnancy (Thorburn and Schneider, 1972). The limited information on cervids indicates that red deer rely on luteal progesterone throughout pregnancy (Kelly *et al.*, 1982) and white-tail deer exhibit a relatively constant progesterone pattern during pregnancy similar to those of goats and cattle (Plotka *et al.*, 1977). Domestic sheep do not require luteal progesterone during the latter half of gestation (Sarda *et al.*, 1973). However, the sheep corpus luteum shows only slight shrinkage 2–3 weeks before term (O'Shea and McCoy, 1988) and active luteal cells persist into the *postpartum* period (O'Shea and Wright, 1985).

The cause of early regression of the muskox corpus luteum of pregnancy is unknown, but it is clear from both the progesterone data and morphological studies that the corpus luteum persists for longer in pregnant than in nonpregnant muskoxen (Rowell and Flood, 1988). The normal ruminant antiluteolytic mechanisms for the establishment of pregnancy (Roberts, 1989) therefore appear to operate in this species. Subsequent luteal regression could stem from a lack of luteotrophic support or through the action of a luteolytic agent.

The complete regression of the only corpus luteum of pregnancy implicates the placenta as the primary site of progesterone production for the remainder of pregnancy. The contribution of adrenal progesterone was not investigated in muskoxen. The stimulated adrenal cortex can produce significant amounts of progesterone in cervids (Jopson *et al.*, 1990), but in domestic sheep, progesterone production by the unstimulated adrenal cortex is minimal (Harrison and Heap, 1978).

The shape of the progesterone profile of pregnancy differs among ruminants, although all show a decline immediately before parturition. In cattle (Stabenfeldt *et al.*, 1970; Dobson and Kamonpatana, 1986) progesterone concentrations rise little, if at all, above those of the luteal phase; in goats (Thorburn and Schneider, 1972) there is a slight increase in progesterone in the last two-thirds of pregnancy; and in all the species of sheep examined – domestic sheep (Bassett *et al.*, 1969; Stabenfeldt *et al.*, 1972; Tsang, 1978); bighorn sheep (Whitehead and McEwan, 1980); Barbary sheep (Hamon and Heap, 1990) – progesterone concentrations rise well above those of the luteal phase in the second half of gestation and tend to peak shortly before term. The muskox progesterone profile is unique among these and the marked decline in concentrations that occurs at 20–22 weeks gestation has no counterpart in other species studied to date.

Fig. 3. Representative photomicrographs of the corpus luteum of pregnancy at 3 stages of gestation. Stained with haematoxylin and eosin. Bar = 35 μm . (a and b) 4–6 weeks gestation. Large luteal cells with prominent nucleoli predominated (a), although some evidence of cell death was found in all corpora lutea at this stage of gestation (arrows, b). (c) 10–12 weeks gestation. Although apparently healthy large luteal cells could still be found, there were few, cell definition was being lost, pyknotic nuclei (black arrow) and karyorrhexis (open arrow) were common features. (d) 16–18 weeks gestation. No luteal cells could be found and the luteal scar consisted entirely of connective tissue and pigment laden macrophages (arrows).

The decline in progesterone concentration does not seem to be homologous with the preparturient shift from progesterone to oestrogen production that occurs in sheep and cattle. In muskoxen the decline occurred 10–12 weeks before term and it is unlikely that it would be initiated by a rise in fetal corticosteroids at this stage of gestation. There is limited evidence that fecal progestagens are abundant in late pregnant muskoxen (Desaulniers *et al.*, 1989). It is, therefore, possible that the sudden reduction in circulating progesterone is caused by an increase in excretion rate or a switch to the formation of a metabolite not recognized by our plasma assay. A detailed description of hormonal

changes immediately before parturition is not possible with the sampling schedule used in this study.

Progesterone concentrations ranging between 3.3 and 11.5 ng ml^{-1} were found in pregnant, captive muskoxen in Norway. On the basis of subsequent calving dates, the blood samples were probably taken at about the time of the fall in progesterone, thus accounting for the large variation observed (Nilssen *et al.*, 1984). Blood samples collected from wild muskoxen in the Canadian Arctic at an estimated 4–6 weeks before calving all had progesterone concentrations consistent with our present findings (Rowell, 1980).

Fig. 4. The relationship between luteal volume and stage of gestation in muskoxen determined by transrectal ultrasonography. The data were accumulated over three breeding seasons (1988–1989, ▲; 1989–1990, ●; 1990–1991, ■). The line drawn through the points is a simple regression ($R^2 = 0.67$, $P < 0.0001$).

Oestrogen concentrations rose in the latter third of pregnancy when progesterone was low. This changing hormonal relationship may be partially attributed to conversion of progesterone to oestrogens. We did not measure oestrone sulfate, although evidence from sheep indicates that sulfate concentrations may greatly exceed those of unconjugated oestrogens, providing an abundant substrate pool for oestrogen production (Tsang, 1978). If this is also true for the muskox then the oestrogen rise in the last few weeks of gestation need not be the immediate result of progesterone metabolism.

The gestation of 235 days (34 weeks) reported here was shorter than the 250 days reported by Alendal (1971) by approximately the duration of one oestrous cycle. This observation was made on free ranging animals and it is possible that they failed to conceive at the observed mating.

Eight of the ten pregnancies for which we have presented endocrine data ended in the normal birth of a healthy calf but in all cases a placentitis of unidentified aetiology was found (Blake and Rowell, 1989). In the normal deliveries the lesions were minimal but in two cases, one malpresentation and one stillbirth, they were extensive. In spite of this, the hormone concentrations and duration of gestation were similar in all the pregnancies and it seems unlikely that the placental lesions have influenced these results.

The close phylogenetic relationship between sheep, goats and muskoxen (Rowell, 1990) and the numerous similarities in their reproductive anatomy and physiology (Rowell *et al.*, 1987; Rowell and Flood, 1988) make the subtly different features reported here all the more intriguing. The fact that muskoxen are also the only member of the Bovidae to have evolved in the extremes of an arctic environment invites speculation on the possible selective advantages that may be conferred on pregnant muskoxen by the unique, early luteal regression and the unusual, triphasic progesterone profile.

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