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Prostaglandin $F_{2\alpha}$ and Progesterone Profiles in Post-partum Cows with Short Luteal Phases

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Bekana M.: Prostaglandin $F_{2\alpha}$ and progesterone profiles in post-partum cows with short luteal phases. Acta vet. scand. 1997, 38, 323-330. – Sequential blood samples were collected at 3 h interval from 3 Swedish dairy cows starting from the day of first post-partum ovulation for 10 consecutive days to describe short luteal phases. All plasma samples were analysed for the concentrations of the main $PGF_{2\alpha}$ metabolite, 15-ketodihydro-$PGF_{2\alpha}$, whereas levels of progesterone were monitored from all morning samples. The day of ovulation was judged when the largest follicle, being monitored by a real-time B mode ultrasound scanner, could not be detected at the next examination. A sustained rise above 0.5 nmol/l of progesterone level was taken as a clear-cut value between non-luteal and luteal phases. Luteal phases of less than 8 days were registered as a short luteal phase during which the cows showed a total of 8 to 11 significantly elevated levels of the prostaglandin metabolite. The number of the significant increases of the metabolite was calculated using a skewness method. Analysis of these significant increases showed the first 1 to 4 episodes without altering the concentrations of progesterone. This would suggest that the developing corpus luteum is refractory in the beginning and thus, to induce luteolysis several $PGF_{2\alpha}$ releases are required. The magnitude of progesterone concentrations during the short luteal phase is lower than the following phases.

corpus luteum; short oestrous cycle.

Introduction

Attempts to improve reproductive efficiency in the post-partum dairy cows are usually limited by prolonged intervals to first ovulation. Recent studies have been focused on the luteal phase which is usually associated with development of a corpus luteum that has a short life span and is commonly known as short luteal phase or as short oestrous cycle (*Hinshelwood et al.* 1982, *Kindahl et al.* 1982, 1984, *Peter & Bosu* 1987, *Zollers et al.* 1989, *Perry et al.* 1991).

The short luteal phase is considered by some researchers as one of the factors that impair the post-partum reproductive performance due to lower plasma progesterone levels as compared to the succeeding luteal phases (*Mortimer et al.* 1983, *Fagan & Roche* 1986, *Eldon* 1991). Others have considered such cycles to be a normal physiological phenomenon since the short lived corpus luteum may play a critical role in the transition from anoestrus to resumption of normal cyclicity by synchronising endocrine and follicular events (*Lamming et al.* 1981, Hunter, 1991, *Flint et al.* 1992). In line with this notion, evidence suggests that the incidence of short luteal phase in dairy cows is found to be higher when the first post-partum ovulation occurs early and decreases with the increasing time from parturition to first ovulation (*Kindahl et al.* 1982, 1984, *Edqvist et al.* 1984, *Larsson et al.* 1984).

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The short lived corpus luteum might be caused by an uncontrolled release of $PGF_{2\alpha}$ and by the fact that the developing corpus luteum is refractory in the beginning. Later on, luteolysis is induced after several luteolytic episodes of $PGF_{2\alpha}$ (*Kindahl et al.* 1982, 1984, *Edqvist et al.* 1984, *Hunter* 1991, *Silvia et al.* 1991, *Flint et al.* 1992). This release of luteolytic $PGF_{2\alpha}$ might occur due to increasing levels of progesterone and to the fact that the endometrium is out of its normal control for the reason that the involutionary period is not completed. As a comparison during the repair process of the endometrium after intrauterine infusion of iodine solution, significant amounts of $PGF_{2\alpha}$ are synthesized and released which can shorten the oestrous cycle by causing premature regression of corpus luteum (*Kindahl et al.* 1977). This would suggest that there is a minimal exposure time of the uterus to progesterone before $PGF_{2\alpha}$ can be synthesized and released. To be able to follow the $PGF_{2\alpha}$ release, frequent blood samples must be collected, and thus the present study is targeted to describe the nature of 3 to 7 days short cycle/luteal phase in 3 post-partum Swedish dairy cows.

Materials and Methods

Animals

The experiment was carried out in 1 second calving and 2 primipara Swedish dairy cows belonging to the Swedish Red and White (SRB) breed. The cows were 2 to 4 years of age, and they all had short luteal phase of 3 to 7 days after the first post-partum ovulation. The animals were housed in individual pens and fed good quality hay and water ad libitum as well as 8 kg of commercial prepared concentrate according to *Eriksson et al.* (1972).

Clinical examinations

The cows were closely observed and clinically examined 3 times weekly (Tuesday, Thursday and Saturday) during the first 8-week post-partum period. Inspection of the vulva and the perineal area, as well as palpation per rectum and ultrasound scanning of the cervix, uterus, and the ovaries were performed (*Bekana et al.* 1996a) to determine the completion of uterine involution and resumption of ovarian activities. The day of ovulation was judged when the largest follicle, being monitored by a real-time B mode ultrasound scanner, could not be detected at the next examination. The subsequent sustained rise above 0.5 nmol/l in the plasma concentration of progesterone was taken as a clear-cut value between non-luteal and luteal phases. The day of first post-partum ovulation was designated day 1 of the short luteal phase. Luteal phase of less than 8 days was registered as a short luteal case.

Bacteriology

Endometrial biopsies were aseptically collected twice weekly (Monday and Friday) according to the methods described previously (*Bekana et al.* 1994) for bacteriological examination during the first 8 weeks post-partum. The subsequent identification of bacterial species were performed according to Bergy's Manual of Systematic Bacteriology (*Holt* 1984, 1986, *Holt et al.* 1994) at the Department of Clinical Microbiology, Swedish University of Agricultural Sciences.

Blood sampling and hormone analysis

As part of another study, about 10 ml of blood samples were collected twice daily via jugular vein puncture (*Bekana et al.* 1996a). Sampling started immediately after parturition and continued until the first post-partum ovulation. Thereafter, sequential samples were collected at 3 h interval for the next 10 consecutive days to describe the nature of the first post-partum luteal phase. After immediate centrifugation, about 5 ml of plasma were removed and stored

in plastic tubes at -20 °C until analysed for the contents of $PGF_{2\alpha}$ metabolite and progesterone.

15-Ketodihydro-$PGF_{2\alpha}$ analysis

All plasma samples were analysed for concentrations of 15-ketodihydro-$PGF_{2\alpha}$ according to *Granström & Kindahl* (1982). The relative cross-reactions of the antibody raised against 15-ketodihydro-$PGF_{2\alpha}$ were 16% with 15-keto-$PGF_{2\alpha}$, 4% with 13,14-dihydro-$PGF_{2\alpha}$, 0.5% with $PGF_{2\alpha}$, and 1.7% with the corresponding metabolite of PGE_2. The lower limit of detection of the assay was 30 pmol/l for 0.5 ml plasma. The inter-assay coefficient of variation was 14% (at 114 pmol/l), and the intra-assay coefficient of variation varied between 6.6% and 11.7% at different ranges of the standard curve.

The duration in hours of the premature luteolytic prostaglandin release was calculated using a skewness method (*Zarco et al.* 1984). All prostaglandin metabolite values pertaining to the short luteal phase were used in the calculation. The higher values were removed from the data set in several cycles which were repeated until no new significant elevations were detected. The plasma levels of the $PGF_{2\alpha}$ metabolite were considered to be significantly elevated as long as they exceeded the mean value plus 2 standard deviations (SD) as previously described (*Bekana et al.* 1996b). The number of elevated levels was counted and no attempts have been made to evaluate if these levels are belonging to the same luteolytic peak or not.

Progesterone analysis

Levels of progesterone were determined from all morning samples according to *Forsberg et al.* (1993). The assay is an enhanced luminescence immunoassay (Amerlite®; Kodak Clinical Diagnostic Ltd; Amersham, England). Serial dilution of bovine plasma with high concentrations of progesterone showed displacement curves parallel to the standard curve. The lowest limit of detection for the assay was 0.2 nmol/l, but progesterone levels above 0.5 nmol/l were considered to be of biological importance. The inter-assay coefficient of variation was below 4%. The inter-assay coefficient of variation calculated from quality control samples was between 4% and 8.1%.

Luteolysis was considered to be initiated at the time the first significant elevated $PGF_{2\alpha}$- metabolite level was observed concomitantly with a continued decline in the concentrations of progesterone, and was considered as completed when the levels reached 0.5 nmol/l or remained below.

Results

The bacteriological examination of endometrial tissue in the 3 cows showed negative results during the first 8 weeks post-partum. The interval from parturition to first post-partum ovulation (hereafter referred to as day 1 of the short luteal phase) was 42 to 51 days. The first post-partum luteal phase was characterised by lower concentrations and/or shorter duration of pro-

Table 1. Main characteristics of the short luteal phase in 3 post-partum cows.

Cow no.	Length of luteal phase (days)	Number of significant elevated levels of $PGF_{2\alpha}$-metabolite			Levels of $PGF_{2\alpha}$-metabolite at 2 SD (pmol/l)
		Prior to luteolysis	During luteolysis	Total	
1	5	1	7	8	306
2	3	0	11	11	286
3	7	4	7	11	357

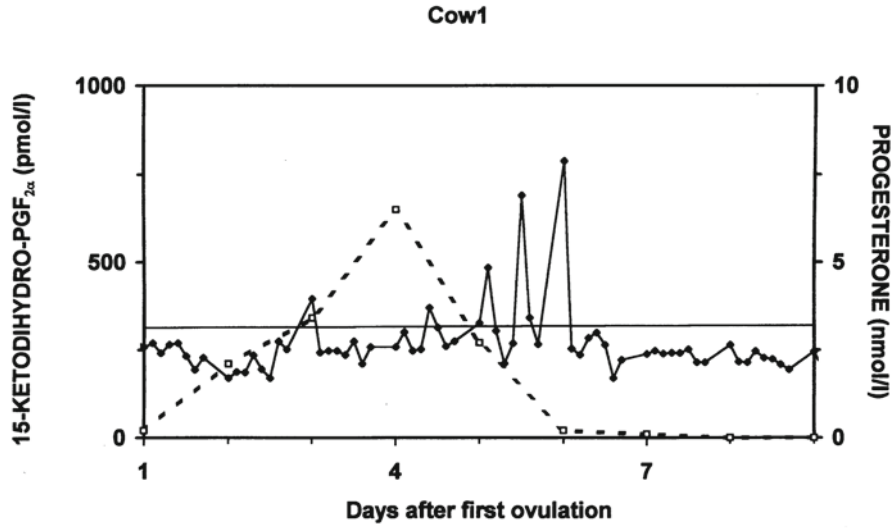

Figure 1. Peripheral blood plasma levels of 15-ketodihydro-$PGF_{2\alpha}$ (——) and progesterone (-----) during the short luteal phase in cow no. 1. The horizontal line in the figure denotes the line of significance (mean basal value + 2 SD) for the prostaglandin metabolite levels.

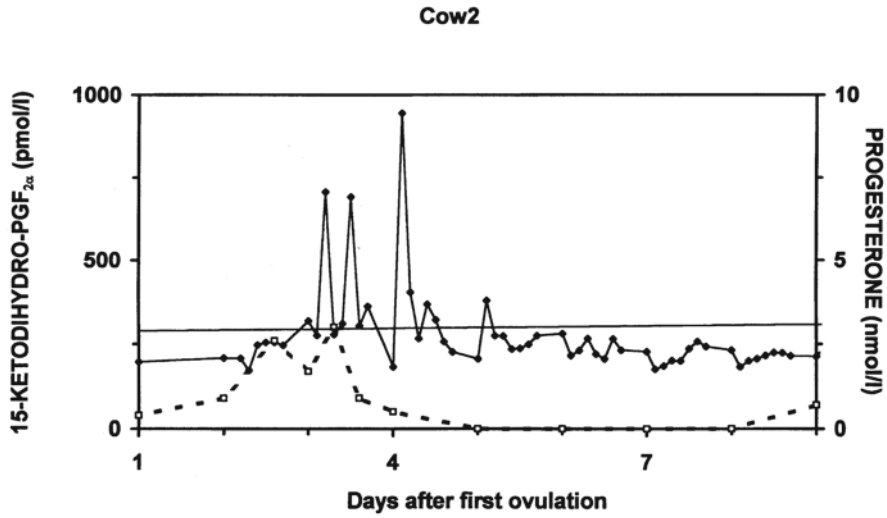

Figure 2. Peripheral blood plasma levels of 15-ketodihydro-$PGF_{2\alpha}$ (——) and progesterone (-----) during the short luteal phase in cow no. 2. The horizontal line in the figure denotes the line of significance (mean basal value + 2 SD) for the prostaglandin metabolite levels.

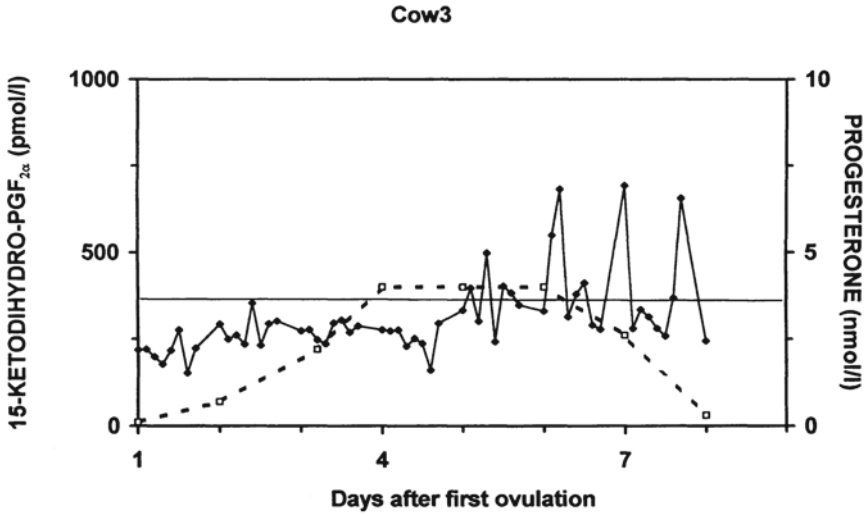

Figure 3. Peripheral blood plasma levels of 15-ketodihydro-$PGF_{2\alpha}$ (——) and progesterone (-----) during the short luteal phase in cow no. 3. The horizontal line in the figure denotes the line of significance (mean basal value + 2 SD) for the prostaglandin metabolite levels.

gesterone production. A decrease in progesterone concentrations below 0.5 nmol/l was noticed in association with several elevated levels of the $PGF_{2\alpha}$-metabolite at different time intervals. Table 1 presents a total of 8 to 11 significant elevations of $PGF_{2\alpha}$-metabolite levels in the 3 cows. The first 1 to 4 of these elevations were not found to be linked to a decline in the concentrations of plasma progesterone.

The plasma progesterone concentrations for cow no. 1 were <0.5 to 6.5 nmol/l during days 1 to 6. Visually, the cow showed 8 significant elevated levels of $PGF_{2\alpha}$-metabolite with different time intervals (Fig. 1). The first increase was found about 36 h prior to the onset of luteolysis and did not appear to result in the initiation of luteolysis. The following 7 elevations were found to be responsible for premature luteolysis. When the 15-ketodihydro-$PGF_{2\alpha}$ was in its highest concentration of 788 pmol/l, levels of progesterone reached below the detection limit, indicating the completion of luteolysis. The length of the luteal phase was 5 days, and the basal level of the 15-ketodihydro-$PGF_{2\alpha}$ was estimated to be 306 pmol/l.

In cow no. 2, the plasma progesterone concentrations varied from <0.5 to 3 nmol/l during days 1 to 4. The cow showed 11 significant elevated levels of $PGF_{2\alpha}$-metabolite in relation to luteolysis (Fig. 2). When 15-ketodihydro-$PGF_{2\alpha}$ was at its highest concentration of 945 pmol/l, levels of progesterone declined from the highest of 3 to approximately less than 0.5 nmol/l. The duration of luteal phase was 3 days, and the basal level of the 15-ketodihydro-$PGF_{2\alpha}$ was 286 pmol/l.

In cow no. 3, the release pattern of $PGF_{2\alpha}$ was very similar to that found in cow no. 1 (Fig. 3). During days 1 to 8, the plasma progesterone concentrations were <0.5 to 4 nmol/l, and the cow showed a total of 11 significant elevated levels of 15-ketodihydro-$PGF_{2\alpha}$. The initiation

of siginificant elevations in the concentrations of 15-ketodihydro-$PGF_{2\alpha}$ occurred about 24 h prior to the onset of luteolysis followed by another 3 elevations which were found prior to luteolysis. The remaining 7 significant elevated levels of $PGF_{2\alpha}$-metabolite were found to be responsible for luteolysis. When 15-ketodihydro-$PGF_{2\alpha}$ metabolite was at its highest concentration of 692 pmol/l, levels of progesterone declined to 2.6 nmol/l around day 7 of the cycle. Further decline in progesterone concentrations was found in association with the following two elevations and the levels reached to a nadir of detection limit on day 8 of the cycle. The duration of the luteal phase was 7 days and the basal level of the 15-ketodihydro-$PGF_{2\alpha}$ was estimated to be 357 pmol/l.

Discussion

Premature luteolysis can be initiated by exogenous administration of $PGF_{2\alpha}$ or by the induction of endogenous release of the compound from the uterus of the cow. Nevertheless, previous studies have shown that the corpus luteum must be of a certain age, about 5 days after ovulation before it is susceptible to the effect of $PGF_{2\alpha}$ (*Lauderdale et al.* 1981). The repair process of the endometrium during intrauterine infusion of iodine solution has also been reported to cause significant amounts of $PGF_{2\alpha}$ synthesis and release within short time (*Kindahl et al.* 1977). This release can induce premature luteolysis with a pattern similar to that observed during spontaneously induced luteal regression. In line with this, the present findings suggest that development of corpus luteum after the first post-partum ovulation shows some initial refractoriness to the luteolytic effect of $PGF_{2\alpha}$, requiring several number of episodes to terminate the life span of the corpus luteum.

In the present study, a total of 8 to 11 significant elevated levels of the $PGF_{2\alpha}$-metabolite have been seen by the use of a skewness method during the 3 to 7 days of short luteal phases. Analysis of these elevations showed the first 1 to 4 successive episodes without altering the concentrations of progesterone. Later on, a more substantial release of $PGF_{2\alpha}$ was found in relation to luteolysis. Thus, the onset of significant increases in the secretion of $PGF_{2\alpha}$ probably does not initiate luteal regression during the short luteal phase, confirming initial refractoriness of corpus luteum to the luteolytic effect of $PGF_{2\alpha}$. Consequently, to obtain a luteolytic effect of $PGF_{2\alpha}$, several different enhanced releases are required and functional luteolysis, which involves a decline in progesterone secretion, begins sometime after the initiation of the first significant elevation of 15-ketodihydro-$PGF_{2\alpha}$ levels. Therefore, sequential sampling at an interval of 3 h is a minimum requirement to describe the pulsatile nature of $PGF_{2\alpha}$ release and the status of corpus luteum and thereby determine the progesterone profile during the short luteal phase. To be able to describe luteolysis in more details e.g. a continuous sampling regimen is needed (*Basu & Kindahl* 1987). The exact reason for the premature prostaglandin release is not known, but should be considered as a physiological phenomenon since the incidence of short cycle is so high (*Edqvist et al.* 1984, *Kindahl et al.* 1984, *Larsson et al.* 1984, *Eldon* 1991) in the process of adapting the uterus or ovaries and their elaborate endocrinological control from acyclic to a cyclic state (*Lamming et al.* 1981, *Fredriksson et al.* 1985, *Perry et al.* 1991). Although a number of luteolytic episodes of $PGF_{2\alpha}$ are required to cause luteolysis as found in the present study, the highest magnitude of the compound is secreted toward the end of the short luteal phase and found in relation to the completion of luteal regression. This enhancement of $PGF_{2\alpha}$ release during the time of functional regression of corpus luteum indicates that the decline in progesterone levels possibly facilitates release of pros-

taglandins and serves to ensure regression of corpus luteum. Cessation of $PGF_{2\alpha}$ synthesis, on the other hand, occurs within a few h after progesterone concentrations are reduced to basal levels. This concept has been demonstrated in heifers which were implanted with progesterone during the luteal phase (*Kindahl et al.* 1979, *Duchens et al.* 1995). Although the initiation of $PGF_{2\alpha}$ synthesis, which leads to luteolysis, was not affected at about day 16, the synthesis of the compound continued for a number of days following corpus luteum regression. This is because progesterone was maintained above basal levels by the implant. With removal of the implant on day 25, progesterone soon declined to basal levels and $PGF_{2\alpha}$ synthesis ceased.

An explanation for the possible cause of the premature luteolysis is an inappropriate controlling mechanism of luteolytic $PGF_{2\alpha}$ production from the endometrium during the postpartum period (*Kindahl et al.* 1982, 1984).

Summing up, development of corpus luteum after the first post-partum ovulation shows initial refractoriness to the luteolytic effect of $PGF_{2\alpha}$, requiring several significant episodic releases to cause the final demise of the corpus luteum, and progesterone concentrations during the short luteal phase are lower than the following phases (*Bekana et al.* 1996a).

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Sammanfattning

Profiler av prostaglandin $F_{2\alpha}$ och progesteron hos kor efter förlossning med korte lutealfaser.

Blodprover samlades var tredje timme från 3 svenska mjölkkor med start från första ovulationen efter förlossningen för att beskriva korta lutealfaser. Alla proverna analyserades med avseende på prostaglandinmetabolit och morgonproverna för progesteron. Ovulationsdagen bestämdes utifrån att en stor follikel inte längre kunde bestämmas med ultraljudsteknik och att progesteronvärdena steg över 0,5 nmol/l. Lutealfaser understigande 8 dagar definieras som korta. Korna visade ett antal om 8-11 signifikanta förhöjningar i prostaglandinmetabolitnivåerna. De första 1-4 av dessa episoder förändrade inte progesteronnivåerna. Detta tyder på att gulkroppen är refraktär mot prostaglandin i början av sin utveckling och att ett flertal prostaglandinfrisättningar behövs för att avsluta luteolysen. Progesteronnivåerna är också lägre i förhållande till vad som syns under kommande östralcykler.

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