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Research

Delayed effect of low progesterone concentrations on bovine uterine $PGF_{2\alpha}$ secretion in the subsequent oestrous cycle

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Low progesterone concentrations during the bovine oestrous cycle induce enhanced responsiveness to oxytocin challenge late in the luteal phase of the same cycle. The delayed effect of low progesterone concentrations during one oestrous cycle on uterine $PGF_{2\alpha}$ secretion after oxytocin challenge on day 15 or 16 of the subsequent cycle was studied by measuring the concentrations of the major $PGF_{2\alpha}$ metabolite (13,14-dihydro-15-keto $PGF_{2\alpha}$; PGFM) in plasma. Two experiments were conducted, differing in the type of progesterone treatment and in the shape of the low progesterone concentration curves. In Expt 1, progesterone supplementation with intravaginal progesterone inserts, with or without an active corpus luteum, was used to obtain high, or low and constant plasma progesterone concentrations, respectively. In Expt 2, untreated cows, representing high progesterone treatment, were compared with cows that had low but increasing plasma progesterone concentrations that were achieved by manipulating endogenous progesterone secretion of the corpus luteum. Neither experiment revealed any differences in plasma progesterone concentrations between the high and low progesterone groups in the subsequent oestrous cycle. In both experiments, both groups had similar basal concentrations of PGFM on day 15 (Expt 1) or 16 (Expt 2) of the subsequent oestrous cycle, 18 days after progesterone treatments had ended. In both experiments, the increases in PGFM concentrations in the low progesterone groups after an oxytocin challenge were markedly higher than in the high progesterone groups. These results indicate that low progesterone concentrations during an oestrous cycle have a delayed stimulatory effect on uterine responsiveness to oxytocin during the late luteal phase of the subsequent cycle. This resulting increase in $PGF_{2\alpha}$ secretion may interfere with luteal maintenance during the early stages of pregnancy.

Introduction

The involvement of progesterone in the regulation of uterine $PGF_{2\alpha}$ secretion is well documented. Most studies have indicated that the episodic secretion of $PGF_{2\alpha}$, which induces luteolysis in sheep and cows, is controlled by the binding of oxytocin to newly formed receptors, particularly in the luminal epithelium, during the late luteal phase of the oestrous cycle (Geisert *et al.*, 1994; Wathes and Lamming, 1995; Mann *et al.*, 1999). Progesterone controls the timing of the development of oxytocin receptors, and addition of exogenous progesterone early in the oestrous cycle inhibited the development of endometrial oxytocin receptors in ewes (Lau *et al.*, 1992) and advanced uterine responsiveness to oxytocin challenge, as estimated from the increase in plasma concentrations of the major metabolite of $PGF_{2\alpha}$ in cattle, 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM; Mann *et al.*, 1998). Mann and Lamming (1995) found that cows with lower concentrations of plasma progesterone during the luteal phase of the oestrous cycle had an enhanced surge of PGFM after oxytocin treatment on days 15 and 16 of the same cycle. It was postulated that a decrease in the concentration of endometrial progesterone receptors in the mid-luteal phase of the oestrous cycle in cattle depressed the inhibition of oxytocin receptor development by progesterone, thereby facilitating the luteolytic secretion of $PGF_{2\alpha}$ later in the cycle (Lamming and Mann, 1995; Wathes and Lamming, 1995). To the best of our knowledge, all the studies published to date have investigated the relationships among progesterone concentration, oxytocin receptor development and uterine $PGF_{2\alpha}$ release within the same oestrous cycle. The possible long-term delayed effect of progesterone in one oestrous cycle on uterine $PGF_{2\alpha}$ secretion in subsequent cycles has not been investigated.

Low peripheral concentrations of progesterone after insemination are related to low fertility of cows (Lamming *et al.*, 1989). This relationship has been hypothesized to be associated with high uterine secretion of $PGF_{2\alpha}$, which may interfere with pregnancy recognition and result in embryo loss (Mann and Lamming, 1995). However, low fertility in cattle is also related to low progesterone concentrations in

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the oestrous cycle preceding insemination (Holness *et al.*, 1981; Fonseca *et al.*, 1983; Folman *et al.*, 1990), which suggests that a delayed effect of low progesterone concentration in the oestrous cycle preceding insemination decreases the subsequent embryo survival rate. The observation of short oestrous cycles in cattle early in the postpartum period, although representing an extreme situation, indicates that there may be a delayed effect of progesterone on uterine function, and shows that lack of a previous luteal phase (and exposure to progesterone) induces early secretion of $PGF_{2\alpha}$ and early luteolysis, resulting in short cycles (Garverick *et al.*, 1992). It is worth noting that various types of stress, for example, a negative energy balance after parturition (Butler, 2000) and hormonal deficiency such as low progesterone secretion (Shaham-Albalancy *et al.*, 1997a), induced pronounced long-term delayed effects on ovarian (follicular and luteal) functions in cattle, several weeks after removal of the stress. There has been no study of a possible delayed effect of low progesterone concentration on uterine function. The aim of the present study was to investigate a possible delayed effect of low progesterone concentrations during the luteal phase of one oestrous cycle on uterine responsiveness to oxytocin challenge, as expressed in terms of $PGF_{2\alpha}$ secretion, at the end of the luteal phase of the subsequent oestrous cycle.

Materials and Methods

Two experiments were conducted, differing in the type of progesterone treatment and in the shape of the low progesterone concentration curves. In Expt 1, high and low plasma progesterone concentrations were achieved by exogenous progesterone supplementation via intravaginal progesterone inserts, with or without an active corpus luteum. In Expt 2, high and low progesterone concentrations were achieved by manipulating endogenous progesterone secretion by the corpus luteum. Other details concerning cows, synchronization of oestrous cycles, detection of oestrus by examination four times a day, oxytocin challenge and hormonal analyses were similar in both experiments. The study was conducted according to the guidelines of the local ethics committee.

Animals

The experiments were performed on multiparous lactating Holstein dairy cows. The cows were in the second half of lactation, of normal cyclicity and yielding averages of 37 and 34 kg of milk per day in Expts 1 and 2, respectively. None of the cows had experienced any noticeable postpartum uterine disorders. Cows were fed *ad libitum* with a complete mixed ration containing 17% (w/w) protein and 1.72 Mcal kg^{-1} in dry matter.

Experimental groups

Experiment 1. Oestrous cycles were synchronized by i.m. injection of a $PGF_{2\alpha}$ analogue (500 μg Cloprostenol; Estrumate; Coopers, Berkhamsted), and cows in which oestrus was detected within the subsequent 72 h were allocated randomly to one of two groups. Cows in the high progesterone group ($n = 5$) were treated to obtain high peripheral progesterone concentrations. These cows maintained an intact, active corpus luteum; they received two intravaginal progesterone inserts (1.2 g; CIDR-B; Eazi Breed, Hamilton), which were inserted on day 6 of the oestrous cycle and replaced 3 days later (day 9) with two new devices. $PGF_{2\alpha}$ was injected on day 12 of the treatment cycle and on the next day (day 13) the intravaginal progesterone inserts were withdrawn and a second dose of $PGF_{2\alpha}$ was injected. Cows in the low progesterone group ($n = 5$) were treated to obtain low and constant concentrations of plasma progesterone. These cows received two $PGF_{2\alpha}$ injections, on days 6 and 7 of the oestrous cycle, to induce regression of the corpus luteum. The intravaginal progesterone inserts were inserted on day 6 of the oestrous cycle, replaced 4 days later with new devices and withdrawn on day 14. The above protocol allowed the cows in the high progesterone group one more day than the cows in the low progesterone group for growth of the preovulatory follicle, to compensate for its slower growth under high progesterone concentrations (Sirois and Fortune, 1990; Savio *et al.*, 1993). Subsequently, both groups underwent oestrus on the same day of the treatment cycle (day 16), and the oxytocin challenge was applied, concurrently, on the same day of the subsequent oestrous cycle.

Experiment 2. Synchronized cows were assigned randomly to one of two groups: an untreated group ($n = 8$), which served as the high progesterone group, and a low progesterone group ($n = 7$). The cows in the low progesterone group were treated to elicit gradually increasing but still low plasma progesterone concentrations. Cows in this group were given three consecutive injections of $PGF_{2\alpha}$ analogue (500 μg Cloprostenol) at 12 h intervals starting on day 3 of the oestrous cycle, as described by Beal *et al.* (1980). This procedure has been used successfully to induce low but increasing progesterone concentrations in two of our recent studies (Shaham-Albalancy *et al.*, 1997b, 2000). On day 18 of the treatment cycle, both groups were given injections of $PGF_{2\alpha}$ to induce regression of the corpus luteum and the cows underwent oestrus within 54–72 h.

Oxytocin challenge

Blood samples for determination of progesterone concentrations were collected from the jugular vein into heparinized Vacutainer tubes on day 6 and then daily from day 9 to day 14 of the treatment cycle in Expt 1 (before insertion or replacement of intravaginal progesterone inserts), and on days 3, 6, 9, 10, 11, 12 and 15 of the treatment cycle in Expt 2. In the subsequent cycle, blood samples were collected on days 6, 9, 11, 13 and 15 or 16. On day 15 or 16 of the subsequent cycle in Expt 1 or 2,

respectively, cows were challenged with a single i.v. oxytocin injection (100 iu vitsintocyn; Vitamed Ltd., Bat-Yam). Blood samples were collected at 15 min intervals from 1 h before to 3 h after the oxytocin treatment for determination of PGFM concentrations. Plasma samples were stored at –20°C for subsequent determination of hormone concentrations.

Hormone analyses

Plasma progesterone concentrations were analysed in a single assay with a solid-phase radioimmunoassay kit (Diagnostic Product Corporation, Los Angeles, CA) using a standard curve prepared in our laboratory by dissolving progesterone in plasma from an ovariectomized cow (Schindler *et al.*, 1990). Antibody crossreactivity was 0.2% with 5β-pregnan-3α-ol-20-one and 2% with 20α-dihydroprogesterone. The assay sensitivity was 0.2 ng ml^{-1} and the intra-assay coefficient of variation was 9.8%. Plasma oestradiol concentrations were determined on the day of oxytocin challenge (day 15) by a previously described single-antibody radioimmunoassay (Badinga *et al.*, 1992), with antibody purchased from Diagnostic Product Corporation that had been validated and used in our laboratory (Shaham-Albalancy *et al.*, 1997b). Plasma PGFM concentrations were analysed according to the validated radioimmunoassay procedure described by Guilbault *et al.* (1984). The specific antibody (gift from W. W. Thatcher, University of Florida) crossreacted with arachidonic acid, PGE_2 and $PGF_{2\alpha}$ by < 1% and with $PGF_{1\alpha}$ by < 1.7%. The assay sensitivity was 2.5 pg per tube and the intra- and interassay coefficients of variation were 4.2 and 8.5%, respectively.

Statistical analysis

Plasma concentrations of progesterone and PGFM were analysed according to the general linear model procedure of the Statistical Analysis System (SAS, 1987). The statistical models included effects of: treatment, cows (within treatment), time (day of oestrous cycle or minutes from oxytocin treatment) and treatment by time interaction. Data on progesterone concentrations for the treated and subsequent oestrous cycles were analysed separately. Data are presented as mean ± SEM.

Results

Experiment 1

Plasma progesterone concentrations in the high progesterone group during the treated oestrous cycle were higher ($P < 0.01$, Fig. 1a) than those in the low progesterone group; on day 12, mean progesterone concentrations were 5.8 and 1.4 ng ml^{-1} in the high progesterone and low progesterone groups, respectively. A treatment-by-day interaction analysis ($P < 0.01$) indicated a pronounced difference between the shapes of the two progesterone concentration curves: that of the high progesterone group was, as expected, high and increasing and that of the low progesterone group was low and constant. The progesterone concentration curves during the subsequent oestrous cycles were similar in the two groups (Fig. 1b). Plasma oestradiol concentrations on the day of oxytocin challenge (day 15 of the subsequent oestrous cycle) were similar in the high progesterone and low progesterone groups (4.3 ± 0.2 and 4.6 ± 0.7 pg ml^{-1}, respectively). Mean basal plasma PGFM concentrations before the oxytocin challenge did not differ between the low progesterone and high progesterone groups (Fig. 2). After oxytocin injection, the mean plasma PGFM concentration was higher ($P < 0.05$) in the low progesterone group than in the high progesterone group (65 versus 29 pg ml^{-1}, respectively). The peak of the PGFM surge (reached 15 min after oxytocin injection) was higher in the low progesterone group than in the high progesterone group (128 versus 79 pg ml^{-1}, respectively). The responses of PGFM concentration to oxytocin, expressed as percentages of the pretreatment PGFM concentrations, resulted in mean

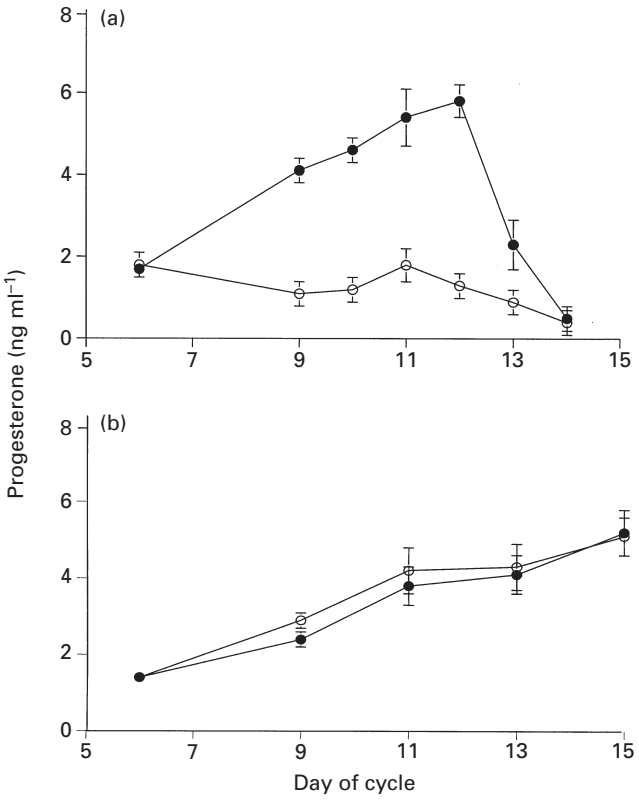

Fig. 1. Plasma progesterone concentrations in Expt 1: (a) during the treated bovine oestrous cycle, when low and high progesterone concentrations were induced; and (b) during the subsequent cycle, when uterine oxytocin challenge was induced on day 15 of the cycle. High or low progesterone concentrations were achieved by intravaginal progesterone inserts in cows with an active corpus luteum (high progesterone; ●; $n = 5$) or without a corpus luteum (low progesterone; ○; $n = 5$). Values are mean ± SEM.

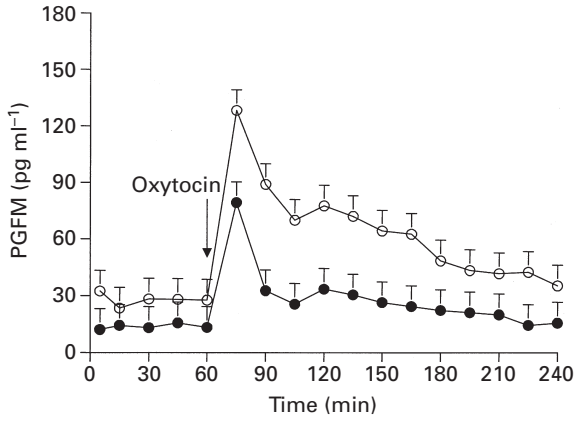

Fig. 2. Plasma concentrations of 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM) in Expt 1, determined from 1 h before to 3 h after oxytocin challenge (100 iu; i.v. injection) on day 15 of the subsequent cycle in cows exposed to high (●; $n = 5$) or low (○; $n = 5$) progesterone concentration treatments in the previous cycle. Values are mean ± SEM.

increases of 260 and 200% in the low progesterone and high progesterone groups, respectively.

Experiment 2

Plasma progesterone concentrations of the low progesterone group increased from day 6 to day 12 of the treatment cycle, but the values were much lower than those in the untreated, high progesterone group ($P < 0.01$, Fig. 3a). On day 12, concentrations were 5.3 and 2.3 ng ml^{-1} in the high progesterone and low progesterone groups, respectively. Similar to Expt 1, the progesterone concentrations during the subsequent oestrous cycle (Fig. 3b) and the plasma oestradiol concentrations on the day of oxytocin challenge did not differ between the two groups. Basal concentrations of plasma PGFM before oxytocin injection in the low progesterone and the high progesterone groups also did not differ between the groups (Fig. 4). After oxytocin injection, the mean PGFM concentration in the low progesterone group was higher ($P < 0.05$) than that in the high progesterone group (101 versus 58 pg ml^{-1}, respectively). The peak of the PGFM surge in the low progesterone group was twice as high as that in the high progesterone group (156 versus 87 pg ml^{-1}, respectively; Fig. 4).

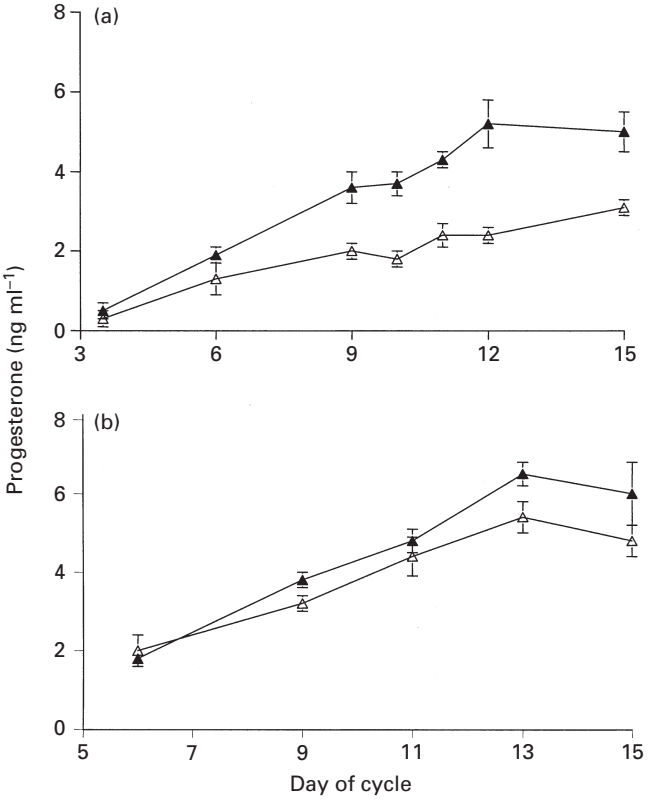

Fig. 3. Plasma progesterone concentrations in Expt 2: (a) during the treated oestrous cycle, when low and high progesterone concentrations were induced; and (b) during the subsequent cycle, when uterine oxytocin challenge was induced on day 15 of the cycle. Untreated cows served as the high progesterone group (▲; $n = 8$). Low progesterone concentrations were achieved by three consecutive injections of $PGF_{2\alpha}$ at 12 h intervals starting on day 3 of the cycle (△; $n = 7$). Values are mean ± SEM.

Discussion

In this study, evidence is presented for the first time of a delayed effect of low progesterone concentrations during one oestrous cycle on uterine $PGF_{2\alpha}$ secretion in the subsequent cycle. The delayed effect of increased $PGF_{2\alpha}$ secretion was observed 18 days after the termination of the period during which the cows were treated to maintain low plasma progesterone concentrations. The patterns, magnitudes and absolute values of plasma PGFM concentrations after oxytocin challenge in cows that had low plasma progesterone concentrations in the previous cycle (present study) were similar to those recorded by Mann and Lamming (1995) on days 15 and 16 of the oestrous cycle in ovariectomized cows that had been treated with progesterone and oestradiol, and which had low plasma progesterone concentrations in the same oestrous cycle.

In the present study, the delayed effects of low and constant (Expt 1) and low and increasing (Expt 2) progesterone concentrations on plasma PGFM concentrations were evident. The low and constant curve was similar to those obtained in studies in which persistence of follicles was induced (Sirois and Fortune, 1990; Savio *et al.*, 1993). The low but increasing curve mimicked naturally occurring low progesterone curves. The two different low progesterone treatments were chosen because marked differences in follicular characteristics and steroid production had been noted previously in dominant follicles developed under similar low progesterone treatments (Shaham-Albalancy *et al.*, 2000). In contrast, both low

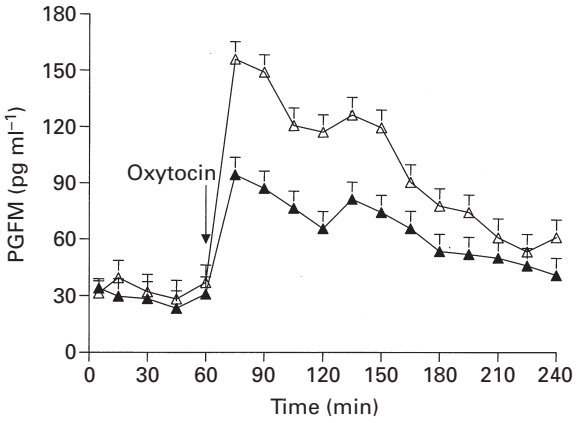

Fig. 4. Plasma concentrations of 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM) in Expt 2, determined from 1 h before to 3 h after oxytocin challenge (100 iu; i.v. injection) on day 15 of the subsequent cycle, in cows exposed to high (▲; $n = 8$) or low (△; $n = 7$) progesterone concentration treatments in the previous cycle. Values are mean ± SEM.

progesterone treatments in Expts 1 and 2 in the present study induced increased uterine responsiveness independent of the shape of the low progesterone curves. During the treatment cycle, the concentrations of plasma progesterone in the high progesterone cows that received two intravaginal progesterone inserts in Expt 1 were, on average, 0.8 ng ml^{-1} higher than those in the untreated high progesterone cows in Expt 2. Such a moderate increase in progesterone concentration induced by intravaginal progesterone inserts is typical of high-yielding dairy cows. A similar increase, of about 1 ng ml^{-1} above that in the control cows, has been recorded previously in cows fitted with intravaginal progesterone inserts and yielding $\geqslant 30$ kg milk day^{-1} (Rosenberg *et al.*, 1990; Shaham-Albalancy *et al.*, 1997b), whereas a 2.4 ng ml^{-1} increase in plasma progesterone concentrations was achieved by insertion of intravaginal progesterone inserts into ovariectomized cows that yielded only 12 kg milk day^{-1} (van Cleeff *et al.*, 1992). Furthermore, the small difference in progesterone concentrations between the two high progesterone groups could be reduced further by the higher milk yield obtained in Expt 1 than in Expt 2.

The mechanism by which low progesterone concentration in one oestrous cycle affects uterine function in the late luteal phase of the subsequent oestrous cycle has not been investigated. In addition, it is not clear why the uterine $PGF_{2\alpha}$ secretory complex is not affected by subsequent exposure to a normally high concentration of progesterone or why the uterine response undergoes no 'correction' in the subsequent oestrous cycle. Nevertheless, the finding that the delayed effect of low plasma progesterone on increased uterine $PGF_{2\alpha}$ secretion in the subsequent oestrous cycle was observed in response to oxytocin challenge indicates that this delayed effect may be related to alterations in endometrial oxytocin receptor concentration or function. In this respect, it should be mentioned that, after oestrus, oxytocin receptors are inhibited by day 5 of the oestrous cycle, after which time a new population develops before luteolysis (Wathes and Lamming, 1995). It is worth noting that, unlike the marked effect of low progesterone on endometrial function observed in the present study, a similar low progesterone treatment (Expt 2) applied in a previous study did not have a delayed effect on endometrial morphology on day 15 of the subsequent oestrous cycle (Shaham-Albalancy *et al.*, 1997b).

The findings of the present study indicate that low fertility in cows that had low plasma progesterone concentrations before insemination (Holness *et al.*, 1981; Fonseca *et al.*, 1983; Folman *et al.*, 1990) might be due to high uterine $PGF_{2\alpha}$ secretion at the time of pregnancy recognition after insemination; this high secretion would lead subsequently to luteal regression and termination of pregnancy. The beneficial effect of pre-insemination exogenous supplementation of progesterone on the fertility of cows and heifers (Rosenberg *et al.*, 1990; Wherman *et al.*, 1993) may be related to decreased $PGF_{2\alpha}$ secretion after insemination, as observed in the high progesterone treatment in Expt 1 in the present study. Furthermore, the fact that low progesterone in one oestrous cycle induced higher $PGF_{2\alpha}$ secretion in the subsequent oestrous cycle, irrespective of the presence of normal progesterone concentrations in the subsequent cycle, may partially explain the ambiguous findings regarding the effect of exogenous progesterone supplementation after insemination on fertility (Diskin and Sreenan, 1986; Macmillan *et al.*, 1999) and regarding the relationship between progesterone concentrations after insemination and embryonic survival (Mann and Lamming, 1995).

Oestradiol also plays an important role in the regulation of uterine $PGF_{2\alpha}$ secretion (Silvia *et al.*, 1991; Wathes and Lamming, 1995). Although the present study concentrated on the delayed effect of progesterone concentration on $PGF_{2\alpha}$ secretion, a possible involvement of oestradiol should also be considered. The likelihood of oestradiol involvement in the uterine response to the low progesterone treatment in Expt 2 is low: in two recent studies, a similar low but increasing progesterone treatment resulted in moderate increases in aromatase activity of granulosa cells and in oestradiol content in the follicular fluid in dominant follicles that were not associated with any increase in plasma oestradiol concentrations during the treatment and subsequent oestrous cycles (Shaham-Albalancy *et al.*, 1997b; 2000). In addition, in the present study, no differences in oestradiol concentrations between treatments were found on the day of oxytocin challenge. However, the low progesterone treatment in Expt 1 (low and constant progesterone curve) has been shown to induce high aromatase activity and a very high concentration of oestradiol in the follicular fluid, associated with an increase in plasma oestradiol concentrations during the treatment cycle (Shaham-Albalancy *et al.*, 1997b; 2000). Therefore, it is possible that in Expt 1 high oestradiol concentrations may

have combined with low progesterone concentrations to enhance the stimulatory effect on the endometrial oxytocin receptor and, subsequently, to increase $PGF_{2\alpha}$ secretion (Beard and Lamming, 1994).

In conclusion, low progesterone concentrations during one oestrous cycle resulted in high $PGF_{2\alpha}$ secretion in the late luteal phase of the subsequent oestrous cycle, and the delayed enhancement of uterine responsiveness in cows with low plasma progesterone concentrations was independent of the pattern of low progesterone secretion. The mechanism responsible for the delayed effect of low progesterone on uterine function is unclear. These data highlight the importance of optimal luteal secretion of progesterone in the cycle preceding insemination for successful conception; low progesterone may interfere with maintenance of the corpus luteum in early pregnancy.

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