The Events of Normal and Abnormal Postpartum Reproductive Endocrinology and Uterine Involution in Dairy Cows: A Review

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SUMMARY

The results of numerous hormonal profile studies in the dairy cow are reviewed with respect to specific hormone changes in the early postpartum period, and factors contributing to the onset of cyclic reproductive activity. Variations from the normal pattern of postpartum hormonal activity or uterine involution are reviewed also. The normal involutionary changes of the bovine uterus are discussed.

RESUME

Une revue de l'endocrinologie reproductive puerperale normale et anormale, ainsi que de l'involution uterine, chez la vache laitière

Cet article présente une revue des résultats de plusieurs études hormonales effectuées chez la vache laitière et relatives aux changements hormonaux qui se produisent dès le début de la période puerperale, ainsi qu'aux facteurs qui contribuent au retour de l'activité reproductrice cyclique. Il passe également en revue les variations du profil normal de l'activité hormonale puerperale et de l'involution utérine. Il présente aussi des commentaires relatifs à l'involution utérine bovine normale.

NORMAL POSTPARTUM REPRODUCTIVE ENDOCRINOLOGY AND UTERINE INVOLUTION

Normal Postpartum Reproductive Endocrinology

A balanced, coordinated endocrine system is important for normal reproductive function. This involves homeostasis among gonadotrophin releasing hormones (GnRH) from the hypothalamus; follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) from the adenohypophysis; prostaglandin F2-alpha (PGF2α) from the uterus and the gonadal steroids (36).

During pregnancy one of the ovaries contains a well developed corpus luteum (CL) and both ovaries have small follicles that are barely detectable on the ovarian surfaces. Occasionally larger follicular structures (≥10 mm) are found. Approximately six weeks prior to parturition, the biosynthetic functions of the fetoplacental unit result in gradually increasing plasma levels of estrogens (11). The peripheral blood level of a metabolite of PGF2α undergoes a dramatic increase shortly before parturition and early in the postpartum period (57). This was viewed as an indication that PGF2α is involved in the prepartum luteolysis of the CL of pregnancy which is in agreement with other reports (15,27).

This increase in PGF2α concentration appears to be extremely important for normal uterine involution. The PGF2α levels parallel the rate of uterine involution with a peak at day 4 postpartum and thereafter remain elevated for up to 20 days (27,31).

Progesterone levels decline rapidly during the last 48 hours before parturition and remain at very low levels (<0.5 ng/mL) throughout the early postpartum period (25,26). This decline is related to regression of the CL of pregnancy.

After parturition, the plasma estrogen levels decrease sharply to values below those found during the normal estrous cycle (18). Increases in estrogen levels have not been reported in the early postpartum period, even though follicular activity is initiated early. It has been suggested that the same feedback mechanism which controls the pituitary during the normal estrous cycle is responsible for initiating the first postpartum estrus (23).

This feedback mechanism involves follicular growth and estrogen secretion. Follicle stimulating hormone is maintained at relatively constant levels throughout the life of the postpubertal dairy cow (50). Plasma FSH concentrations fluctuate between 30 and 70 ng/mL and are somewhat independent of other hormonal changes. Follicle stimulating hormone release, in response to exogenous GnRH injections, is reduced during the period from nine days before to six days after parturition (49). It has been demonstrated also that FSH levels are slightly increased and are maintained at constant levels through parturition and into the postpartum period (13). Thus, it would appear that delay of onset of cyclic function is unlikely to be due to low FSH levels.

Several investigators have studied LH concentrations during various reproductive stages. Luteinizing hormone follows a release pattern that is characterized by a rapid increase followed by a more gradual return to normal levels (3,44). These spasmodic episodes of rapid increase in LH level are described as pulsatile LH release (20). A tonic release maintains basal LH levels. Superimposed on this release pattern is a rapid and marked increase in basal LH levels just prior to ovulation. This has been called the preovulatory LH surge. The same basic LH concentrations and release patterns found during the normal estrous cycle have been observed in cows during the early postpartum period (6,20,49,61).

Follicular activity has been detected as early as five to ten days postpartum (48). The follicles continue to grow until at least one becomes ready to respond to a preovulatory LH surge. Extensive investigation has been necessary to accurately determine the
factors which initiate the first postpartum ovulation. It has been suggested that the ovary regulates LH secretion in cattle (44). However, from studies in primates, it has been proposed that LH secretion, and ovulation are under neural control (30).

In sexually mature female cattle, both estradiol 17-beta (51) and GnRH (49) can induce the release of LH from the anterior pituitary gland. The interaction of these two hormones to cause a LH surge depends primarily on the estradiol 17-beta concentration. Ovariectomized heifers display only a pulsatile LH release pattern (3).

Gradually increasing estrogen concentrations to markedly elevated levels may have an inhibitory effect on the production and/or release of a LH surge by the pituitary. This effect has been demonstrated in late pregnancy and in animals with cystic ovarian disease and is different from the effect of a synchronous rapid elevation in estrogen during late proestrus of the normal cycle. Firstly, in late pregnancy from 40 to 60 days prepartum until six days after calving, estrogen levels are high and there is a decrease in LH peak values. Several workers have examined the pituitary response to exogenous GnRH during the prepartum and postpartum periods and have described LH release in response to GnRH injection to be substantially reduced from five weeks before until eight to ten days after parturition (19,26,49). Full responsiveness returned by day 10 postpartum. A full LH response has been artificially produced at day 2 postpartum by using a combination of estrogens, progesterone, and then, GnRH (2). Secondly, elevated estrogen levels have been found in cows with ovarian cysts (24). Such animals have elevated basal levels of LH, but no LH surge (38). This negative feedback activity is in contrast to the one day estrogen peak that occurs during a normal estrous cycle which is followed by the preovulatory LH surge (23).

On the other hand, high levels of progesterone appear to suppress the hypothalamus and not the pituitary. Progesterone levels are constantly elevated during gestation (42), except for a small decrease from day 60 to day 90 after conception (47). Yet, the pituitary can fully respond to exogenous GnRH throughout pregnancy (49).

In summary, the endocrine changes responsible for the resumption of postpartum cyclic activity are complex. A particular set of hormonal circumstances are necessary for the first postpartum cycle to be initiated. After a short-term elevation, plasma progesterone levels must be low and estradiol 17-beta must be at an appropriate threshold level (51). The rise and decline of progesterone, followed by the rise in estradiol 17-beta that occur prior to the first postpartum cycle, are similar to the changes during proestrus of a normal estrous cycle. It is speculated that GnRH initiates the preovulatory LH surge in late estrus. The presence of a large mature follicle is necessary for all of these changes to occur and the ovulation which follows.

The need for specific hormonal conditions to precede and induce ovulation is supported by the research on the use of GnRH in the early postpartum period (21,26). In one of these studies the ovaries were examined by laparoscopy, and then the cows were treated with GnRH. Induced ovulation occurred only if a large follicle (> 10 mm) was present on the ovary (21).

The first ovulation usually occurs between ten and 25 days postpartum (33,40). Approximately 50% of cows exhibit short cycles during the early postpartum period (39,50). It has been suggested that immature corpora lutea may be the cause of these short cycles (39). The first postpartum endogenous preovulatory LH surges have been shown to be too low to produce complete luteinization (14). It is also possible that reduced blood flow to the ovary may interfere with normal CL formation as has been demonstrated in sheep (41).

The CL of pregnancy is still palpable on the ovary until ten to 14 days postpartum, even though functional activity ceases before parturition (40). The regressed CL of pregnancy does not appear to influence the timing of the first postpartum ovulation. Short-term increases in plasma progesterone have been reported prior to the initiation of the first cycle, which are speculated to be from luteinized follicles (61). These workers suggest that a delay in the time of first ovulation may be due to suppression of GnRH activity by these small increases in progesterone (61). This might, in turn, inhibit pulsatile LH release.

Hormonal profiles of the first estrous cycle have been described in great detail (14). Few endocrinological differences exist compared to subsequent estrous cycles (62). The estradiol levels preceding first estrus were lower than in subsequent cycles. Likewise, LH levels during the first estrus and progesterone concentrations following first ovulation were comparatively lower (50,53).

The ovary ipsilateral to the non-gravid horn has been shown to resume activity more rapidly (33). When ovulations occurred between day 10 and day 15 postpartum, 90% of these ovulations were on the ovary contralateral to the gravid horn. Whether this is due to a local inhibitory effect of the CL of pregnancy or a uterine inhibitory effect of reduced bloodflow remains a matter for speculation.

Several studies indicate that few animals (< 30%) show behavioral signs of estrus accompanying first ovulation (5,28,29). The incidence of silent estrus decreases to less than 30% at the second and third ovulatory cycles (5).

In beef cows, the return to cyclic ovarian function is markedly delayed, the cause of which is poorly understood. The presence of a sucking calf postpones the commencement of cyclic activity (43). Suckling inhibits the pulsatile release of LH and assures continued high PRL levels. In dairy cows, PRL increases at parturition (11), but declines to lower levels within two or three days of calving (58). Elevated PRL levels have been recorded in a selected group of higher producing dairy cows (57). The suppression of PRL does not alter the rate of return to cyclic function (49). Thus, its role in controlling the onset of cyclic activity is suggested to be minimal.

Normal Postpartum Uterine Involution

Several authors have described normal and abnormal involution of the uterus (4,22,39,40,45,46,55).

Shorty after parturition, the uterus is a large organ measuring roughly one meter in length and weighing 8 to 10 kg (46). The most profound involution occurs between the time of calving and day 3 postpartum (38). The rapid
decrease in size is due to vasoconstriction and peristaltic contractions, which occur at three to four minute intervals and gradually diminish by day 4 postpartum.

Events during involution of the uterus include necrosis of the caruncular stalk, breakdown of the superficial layer of the caruncle and formation of the lochial discharge (22,46). This process is generally complete by day 12 postpartum. Normal involution can be an aseptic process, but this is the exception rather than the rule (34).

Spontaneous puerperal infection, with massive bacterial growth in the lochia, is common (45). It has also been reported that 93% of bovine uteri are infected up to day 15, 78% up to day 30, 50% up to day 45 and 9% up to day 60 postpartum (16). Corynebacterium pyogenes and Escherichia coli are the most commonly cultured bacteria.

An extensive study of postpartum involution of the uterus and cervix has been carried out (40). The size of the bovine uterus decreases slowly between days 4 and 9 postpartum. At this time, the diameter of the previously gravid horns ranges from 12 to 14 cm in normal cows and by day 10 the uterus could be completely defined by rectal palpation. Normal cows exhibit a marked increase in uterine tone and decrease in uterine size from days 10 to 14 postpartum which coincide with the onset of first estrus. The uterine horn averages 7 to 8 cm in diameter by day 14. Subsequent involution was rapid and by day 25 a diameter of 2 to 4 cm was usually attained with the uterine horns being almost equal in size (40).

Regression in uterine weight, in a similar pattern and proportion to the reduction in size, has been reported (34). Histological evidence of repair of the endometrium is reported to proceed at a slightly slower rate than gross uterine involution (32).

Involvement of the cervix is slower than that of the uterus (40). Normal cows, on average attain complete cervical involution by day 30 postpartum.

Abnormalities of reproductive endocrinology and uterine involution in the early postpartum period

Abnormal hormonal (7,10,18) and uterine involution changes (40,55) during the early postpartum period have been reported.

Primary predisposition of cows to retained placenta (RP) has been associated with numerous infectious, nutritional, genetic and physiological etiologies. However, it has been suggested that these predisposing factors could lead to a common prepartum temporal change of certain hormones (7). Synchronized hormonal changes have been described in relation to lactogenesis (11), parturition (17), and placental release (10). Interference with these changes by ovarioectomy during pregnancy has resulted in a high frequency of RP (8,37). Similarly induction of premature parturition by glucocorticoid therapy has been associated with a high incidence of RP (9,37,60).

Hormonal profile studies have demonstrated that prepartum plasma progesterone values were elevated in RP cows compared to non-RP cows that calved either spontaneously (1,10) or following glucocorticoid induction (9). Prepartum plasma estrogens were lower in RP than in non-RP cows either after both spontaneous and induced parturition (7,8).

The balance between plasma levels of progesterone and estradiol 17-beta on day 6 prepartum was significantly associated with the subsequent occurrence of RP (7). When plasma progesterone was at an intermediate level (4 to 8 ng/mL) and estradiol 17-beta was high (exceeding 99 pg/mL) there was a tenfold lower incidence of RP than when progesterone was high or when progesterone and estradiol 17-beta were both low. Plasma profiles of PRL and estrone were almost identical in RP and non-RP groups. This experiment was conducted as a case control study with peer matching on several parameters (7).

It has been demonstrated that cows with prolonged uterine involution times also had relatively extended periods of elevated plasma PGF2α levels in comparison to cows with normal uterine involution times (15,31).

The fetoplacental unit produces large amounts of estrogen in late pregnancy, which sensitizes the myometrium to both oxytocin and prostaglandin. A decrease in the estradiol 17-beta/17-alpha ratio has recently been reported to result in a reduced rate of release of prostaglandins from the uterus and a slower rate of uterine involution (18). In other words, a lower concentration of biologically active estrogens may result in a slower rate of involution possibly due to reduced PGF2α release. In this regard, an increase in PGF2α release into the utero-ovarian vein occurred in response to the administration of estradiol 17-beta in the goat (12).

Uterine involution is more rapid in suckled beef cows than in milking dairy cows (48). Involution was complete in 15 to 25 days in suckled cows and in 25 to 30 days in milking cows. The sucking stimulus was believed to cause frequent release of oxytocin from the posterior pituitary, which enhanced the reduction in size of the uterus through its myometrial contractile effect. Milking also causes oxytocin release, but the frequency would be less than that with suckling. It has been shown that milking Holstein cows four times a day until day 25 postpartum improved uterine involution, without affecting the pulsatile LH release and the onset of first estrus (6).

Normal uterine involution and regression of cyclic ovarian activity progressed more slowly in cows with periparturient diseases, such as dystocia, milk fever, ketosis, RP and metritis, than in cows which had experienced normal parturition (40). The uterus did not reach nongravid size until approximately day 30 in cows with such diseases. The uterus was significantly larger at ten and 20 days postpartum after an abnormal parturition. Similar results have been reported by other investigators (4).

Shortly after 30 day postpartum, the differences in involutionary status between cows which had calved normally and those with periparturient abnormalities, were no longer detectable (40). Age and parity are important considerations when evaluating the size of uterine horns on a postpartum examination (4,39). Other authors have also shown that RP significantly delayed uterine involution (34).

Prolonged luteal function has been demonstrated in cows with pyometra (52). It was hypothesized that this might result from failure of PGF2α synthesis due to endometrial damage. It is

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and had longer calving to 70 more 30 first and occurred 31-60 days during formed of tum incidence of anestrus. Incidence commencing the cows not after of subsequent ovulation. It was found that 57 of 69 cows established early regular cycles and their ovarian activity was considered normal. However, the duration of the estrous cycles in some of the normal cows was considered aberrant, being less than 17 days or more than 25 days in length. The incidence of aberrant cycles was 25% after first ovulation, 12% after second ovulation and 8% after third ovulation (27).

The 12 abnormal cows in this study presented a wide variety of postpartum abnormalities (27). Follicular cysts, with plasma progesterone levels of less than 1 ng/mL, were observed following none, one or two normal ovulations. Smooth nonfunctioning ovaries resulted after failure of CL formation subsequent to first ovulation in one case studied. Even in the absence of clinical uterine pathology, a persistent CL was occasionally found after first or second ovulation. All cows commenced the postpartum period with basal plasma progesterone levels, indicating the CL of pregnancy did not remain functional after parturition (27).

Others have reported similar findings using the milk progesterone assay (5,35,59). Incidence rates of 5 to 10% were found for both ovarian cysts and postpartum anestrus.

It has been found that a normal CL formed during only 62.5% of postpartum cycles (40). A CL was considered indicative of a normal estrous cycle. Follicular ovarian cysts developed during 12.3% of the observed cycles and occurred more frequently in the first 30 days postpartum than in the 31-60 day period. Spontaneous recovery, however, was common (40).

Differences between cows with periparturient diseases and cows that calved normally were also reported (40). Ovarian cysts were more common in the former group. They also required more services per conception and had longer calving to conception intervals than the normal cows. The authors emphasized that normal cows had two ovulations during the first 30 to 35 days after parturition, whereas cows with periparturient diseases had only one ovulation during this period (40). These findings were in agreement with the results of other workers (33) and are important in view of the finding that the number of cycles prior to day 30 postpartum was an important indicator of reproductive performance (56).

It is evident from this review of reproductive endocrinology and uterine involution of the postpartum dairy cow that normal ranges have been extensively described. Reports of hormonal values and uterine events are less frequently reported with respect to abnormalities of the postpartum period, such as might exist in cases of retained placenta or metritis. The underlying endocrinological mechanisms necessary for initiation of cyclic ovarian activity after parturition are still not well understood and the reasons for the delay or advancement of resumption of reproductive activity are poorly described. Many questions remain to be answered concerning the postpartum period of the dairy cow. For example, resumption of cyclic ovarian activity in RP cases has not been well documented. Concurrent hormonal profile studies and reproductive tract examinations could provide useful information on this important period in the reproductive life of both dairy and beef cattle.

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