Normal Uterine Physiology and Involution

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Introduction

A 12 to 13 month calving interval should be the goal of dairymen and veterinary practitioners who want to maximize both breeding and milk production efficiency. Such a calving interval will maximize milk yield per day for the interval between calves, maximize total lifetime production of the cow in the herd, and enhance number of potential replacements. To maintain a 12-13 month calving interval, cows must become pregnant within 85 to 115 days after calving. A waiting period of 45 days postpartum is usually recommended prior to first insemination, and this leaves a 40 to 70 day breeding period. Thus, cows must be observed in heat, inseminated, and become pregnant within one to three estrous cycles after breeding begins. It is obvious that proper restoration of the postpartum uterus to a fertile condition and accurate detection of estrus are the two constraints limiting the goal of a 12 to 13 month calving interval. The objective of this presentation is to describe specifically the normal physiology and involution of the postpartum uterus in dairy cows.

Postpartum Uterine Involution

The general classification of the bovine placentae is: cotyledonary, epitheliochorial and delayed deciduate. A placentome is the union of cotyledon (cluster of chorio- allantoic villi; embryonic in origin) and caruncle (mass of septa from caruncle) tissue components. In the epitheliochorial attachment, there is contact and fusion between the chorio-allantoic ectoderm and uterine epithelium. However, the uterine epithelium has not been destroyed¹. In the cow at parturition, when the cotyledonary villi pull out of the caruncular mass, they leave a mass of tissue which is too much to be contracted back into the endometrium, but is not massive enough to tear off at parturition. The large blood vessels in the endometrium constrict at the base of the caruncle and close off the circulation to the septa. This results in cellular necrosis and sluffing of all of the maternal cells that have been involved actively in the placentome. The septal caruncular mass is lost at 5 to 10 days after parturition, whereas in the true deciduous type placentae the maternal tissue involved in the placenta is lost acutely after passage of the fetus.

Immediately following delivery of the feto-placental unit, the large postpartum uterus undergoes dramatic morphological and histological changes that lead to reestablishment of a uterine milieu conducive to initiating a pregnancy. Several reviews and original articles were utilized to summarize these dynamic changes. Gier and Marion described uterine involution as being comprised of three overlapping processes: reduction in size, loss of tissue and repair of tissue.

Gross Morphological Changes

Rectal palpation of the postpartum uterus has been the method used most commonly to estimate the time interval from parturition to complete uterine involution. The uterus was considered to be involuted when it had returned to its normal, nongravid position, and when the two uterine horns were similar in diameter, and were showing normal consistency and tonus, or when the two uterine horns have returned to nongravid size. Generally, one or more of these criteria have been used to study the process of uterine involution by rectal palpation of the uterus. Intervals between palpations ranged from a few days to approximately 2 weeks; undoubtedly, this contributes to the
marked variation in reported intervals for the period of completed involution (range of 18 to 50 days).

Early reduction of uterine size after calving results from vasoconstriction and peristaltic contractions that persist for several days. Guilbault et al. monitored blood flow to the previous gravid uterine horn, with electromagnetic blood flow transducers, in five postpartum cows. Mean blood flow (ml/min) decreased from 3078±683 on day 1 postpartum to 602±56 on day 2 and was 413±55 on day 5. Martin and coworkers monitored postpartum uterine motility by utilizing a catheter which was fluid-filled and inserted into the previous gravid uterine horn and connected to a pressure transducer, amplifier, and recorder system. Recordings were made at 1, 6, and 48 hours postpartum for a period of 20 minutes each in seven normal cows. Measurements of uterine contractility are summarized in Table I. It is strikingly clear that the uterus is quite active during the immediate 2 day period following parturition. Frequency, amplitude, and duration of contractions were highest at 1 hour postpartum and decreased (P<.05) progressively until 48 hours. Undoubtedly, the physiological and endocrine events associated with parturition (loss of calf and placenta; increase in oxytocin and prostaglandin secretions) contribute to the reduction in uterine blood flow and enhanced uterine contractility.

Weight and size of the uterus decrease postpartum in similar patterns. Weight of the uterus of calving was approximately 9 kg and .85 meter in length. Uterine weight comprised of both normal and degenerated cells from the previous gravid uterine horn, and connected to a pressure transducer, amplifier, and recorder system. Recordings were made at 1, 6, and 48 hours postpartum for a period of 20 minutes each in seven normal cows. Measurements of uterine contractility are summarized in Table I. It is strikingly clear that the uterus is quite active during the immediate 2 day period following parturition. Frequency, amplitude, and duration of contractions were highest at 1 hour postpartum and decreased (P<.05) progressively until 48 hours. Undoubtedly, the physiological and endocrine events associated with parturition (loss of calf and placenta; increase in oxytocin and prostaglandin secretions) contribute to the reduction in uterine blood flow and enhanced uterine contractility.

Weight and size of the uterus decrease postpartum in similar patterns. Weight of the uterus of calving was approximately 9 kg and .85 meter in length. Uterine weight was reduced to approximately 3 kg by 10 days, to 1 kg by 20 to 30 days, and to 750 g by 50 days postpartum. The maximum amount of uterine lochial fluid (1,000 to 1,600 ml) is present during the first 48 h and then decreases to 400 to 100 ml between days 10 to 20, and is absent by approximately 24 days postpartum. Lochial fluid was comprised of both normal and degenerated cells from the tunica mucosa and caruncles and from bleeding occurring during shedding of the fetal membranes.

**TABLE 1. Measurements of uterine contractility during the 48 hour period following parturition in seven cows.**

<table>
<thead>
<tr>
<th>Response</th>
<th>1 h</th>
<th>6 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of contractions in 10 min (A)</td>
<td>2.71±.48</td>
<td>1.64±.89</td>
<td>.92±.05</td>
</tr>
<tr>
<td>Amplitude (mm Hg) of all contractions (B)</td>
<td>21.07±5.04</td>
<td>17.14±10.60</td>
<td>6.72±7.16</td>
</tr>
<tr>
<td>Duration (min) of all contractions (C)</td>
<td>1.60±.35</td>
<td>1.18±.63</td>
<td>.83±.85</td>
</tr>
<tr>
<td>Alexandria Units (A x B x C)</td>
<td>95.80±40.46</td>
<td>42.67±27.38</td>
<td>19.95±31.23</td>
</tr>
</tbody>
</table>

* Differences due to time significant for all responses; P<.05. Martin, L. R., et al., Theriogenology 15(5):513-524, 1981.

**Histological Changes Associated With Tissue Loss and Repair**

During the period of rapid decrease in uterine weight and size, intrauterine tissues undergo marked structural changes. On the day after calving, the intercaruncular endometrium became highly edematous. This condition regressed slowly during the next 4 to 5 days. By day 8, endometrial edema had receded and the endometrium was folded leaving the caruncles in a general "stalked" appearance. Riesen et al. reported that the earliest portion of the postpartum interval (approximately the first 20 days) was marked by destruction of endometrial tissue that was accompanied by presence of large numbers of leucocytes and reduction in endometrial vascular bed. Wagner and Hansel indicated that the intercaruncular endometrial epithelium (day 14 postpartum) was highly proliferative in appearance, had lost its normal columnar arrangement, and was several cells thick.

In cattle, expulsion of the fetal membranes usually occurs within 12 h after parturition, and the maternal part of the placentome (caruncle) eventually is lost during the postpartum period. On the day after calving, caruncles, which are more numerous in the previously gravid uterine horn, averaged 70 mm in length, 35 mm in width and 25 mm in height. They consisted primarily of a crumpled mass of septum and blood vessels capping an endometrial base. The gradual disappearance of the caruncular endometrium was described as follows: by day 3 postpartum, caruncles in the previously gravid uterine horn did not show appreciable changes in either size or tissue organization from the prepurient condition; only by day 5, necrosis and complete septal disorganization was associated with vasoconstriction and infiltration by leucocytes; by day 12, most of the caruncular septum had sloughed, leaving a raw surface with protruding remnants of blood vessels; by day 15, sloughing was completed down to the stratum compactum; by day 19, caruncles appeared as rough knobs (15 to 20 mm in diameter) each containing a regressing mass of blood vessels.

Histological studies further substantiated these gross observations and also indicated that the necrotic stage is not attained before day 5 postpartum after which time degeneration of the caruncular mass occurred rapidly. Archbald et al. described the sequence of events involved in regression of the caruncular mass as being initiated by degenerative vascular changes which are followed by peripheral ischemia, necrosis and sloughing. Progressive degenerative vascular changes were observed from days 1 to 19 postpartum. These changes consisted of hydropic degeneration of the cytoplasm and pyonosis of the smooth muscle cells of the tunica media and fibrinoid necrosis of the tunica media. Vascular changes were confined to the tunica media and luminal patency was a constant finding. Although vascular changes were initiated on the day after parturition, necrosis was not observed until day 5.
surface on days 1, 3 and 6, and only after the necrotic process had been initiated was the superficial layer of the caruncle with its epithelium sloughed. Wagner and Hansel indicated that the sloughing of the caruncular endometrium appears to begin at levels just basal to the crypt.

Through radiographic examinations of involuting uteri, Hutchinson and Johanns et al. illustrated that vasoconstriction of the caruncular blood vessels leads to progressive regression of the caruncular endometrium. Vasoconstriction of the caruncular blood vessels, which occurred within 12 h after parturition, was not seen uniformly among the different caruncles. Some caruncles showed an almost complete lack of a blood supply while others maintained the major vascular appearance observed during pregnancy. On day 7 postpartum, size of the caruncle was reduced appreciably, and caruncular arteries were highly constricted or even in a state of degeneration.

Moller identified two pathways by which waste products of uterine involution were eliminated. The regressing cells of the tunic serosa and subserosa, stratum vasculare and myometrium were removed by resorption via the vascular system. In contrast, most of the epithelial cells of the uterine mucosa, from the intercaruncular and caruncular endometrium, were shed by desquamation into the uterine lumen and became part of the lochial fluid.

Factors Affecting Uterine Involution

Various physiological, hormonal and environmental factors may influence uterine involution. Average interval to uterine involution was longer for pluriparous (40.6 days) than primiparous (34.0 days) cows. Similar observations have been reported by Morrow et al. A seasonal effect on uterine involution was reported; uterine involution was more rapid during the warm than cold seasons. The net effect of nutrition on uterine involution appeared minimal. High levels of energy or protein slightly hastened or did not have an effect.

Wagner and Hansel concluded that suckling did not hasten uterine involution. However, in detailed morphological and histological studies of postpartum uteri collected at various intervals postpartum, Riesen et al. and Lauderdale et al. showed that suckling accelerated several processes involved in uterine involution.

Periparturient clinical problems such as dystocia, retained placenta, uterine infection, milk fever and ketosis tend to prolong uterine involution. It was estimated that abnormal clinical conditions may delay uterine involution by 5 to 8 days; these delays may be due to a decrease in uterine motility immediately after parturition or associated with a heavy leucocyte infiltration within the uterine wall. A recent report indicated that retention of fetal membranes was not a result of the lack of uterine contractility during the early stages postpartum.

Uterine involution may be influenced by the endocrine milieu. Fosgate et al. found a delay in involution time in cows treated with 17α-hydroxyprogesterone (100 mg) on alternate days. Progesterone (50 mg) given daily prolonged
utereinvolution, whereas ovariec- tomy hastened involution. Britt et al. and Fernandes et al. demonstrated that an injection of GnRH (Gonadotrophin Releasing Hormone) on day 14 postpartum accelerated the reduction in size of the uterus between 14 and 24 days postpartum.

Postpartum Uterine Secretion of Prostaglandin \( F_{2a} \) (PGF\( F_{2a} \))

The final demise of the corpus luteum (CL) just prior to parturition is associated temporally \( \text{with an increase in PGF}_{2a} \), as measured by high concentrations of 15-keto-13, 14-dihydroprostaglandin \( F_{2a} \) (PGFM) in peripheral plasma. Thus final regression of the CL probably is due to the luteolytic action of PGF\( F_{2a} \). The major increase in concentrations of PGFM in maternal plasma occurred 1 to 4 days postpartum with mean concentrations becoming basal by 10 to 20 days postpartum. A uterine source of PGF\( F_{2a} \) was likely since the postpartum increase was coupled closely with delivery of calf and placenta, and the postpartum decrease in PGF concentrations was correlated \( (r=.68; \ r=.64) \) with uterine horn diameter monitored per rectum in two experiments. Britt et al. and Fernandes et al. demonstrated that an injection of GnRH on day 14 postpartum accelerated the reduction in size of the uterus between 14 and 24 days postpartum.

It is highly probable that the postpartum uterine production of PGF\( F_{2a} \), as monitored by peripheral PGFM concentrations, is related to the involutionary processes of the uterus. In particular, tissue loss or necrosis of the septal area of the caruncle (endometrial epithelium and vascular components; see histological changes) may be associated with PGF\( F_{2a} \) production. One could then deduce that the degree of caruncular development and subsequent amount of postpartum necrosis may determine the extent of uterine PGF\( F_{2a} \) production. One physiological effect of PGF\( F_{2a} \) is its ability to stimulate smooth muscle contractility. Consequently, the massive postpartum release of PGF\( F_{2a} \) may be important for uterine involution.

We have conducted a series of experiments that have manipulated the postpartum profiles of PGFM in dairy cows and related these changes to uterine involution and ovarian activity. An environmental heat stress during the last trimester of pregnancy caused reductions in calf birth weight and increased postpartum concentrations of PGFM. Higher concentrations of PGFM were associated with a faster rate of uterine involution (as measured by return of uterus to its normal nonpregnant position within the pelvic canal). Alteration of conceptus genotype also influenced postpartum uterine function.

Holstein heifers \( (n=7) \) inseminated to Angus bulls had lower calf birth weights and lower postpartum concentrations of PGFM (Figure 1) than heifers inseminated to Holstein \( (n=7) \) or Brahman bulls \( (n=7) \). From the first day that measurements of uterine horn diameter were made (day 5 postpartum) until day 32 postpartum, profile of reduction in mean uterine horn diameter was lower in first calf heifers of the Angus service sire group than in heifers of the Holstein and Brahman service sire groups (Figure 2). Daily rate of reduction in mean uterine horn diameter was similar in the Holstein and Brahman service sire groups and appreciably higher than in the Angus service sire groups (Figure 2). Cervical diameter was closely correlated with uterine horn diameter \( (r=.82) \) and agrees with the observation of Fonseca et al. Higher profiles of PGFM concentrations in Brahman and Holstein service sire groups were associated with a faster rate of uterine involution.

An additional approach to manipulate the postpartum concentrations of PGFM was to suppress the endogenous production of prostaglandins and evaluate subsequent uterine and ovarian responses. On the day of parturition, 18 Brown Swiss cows were assigned randomly to three groups: Group I (FM + Saline) received twice daily injections \( (1 \text{ g/IM of Flunixin Meglumine (FM)) until day 6 and were infused continuously for 10 days with .9% saline into the descending aorta via a catheter inserted into the dorsal costoabdominal artery; Group II (FM + PGF\( F_{2a} \)) received similar FM injectons but were infused continuously for 10 days with PGF\( F_{2a} \) \( (1 \text{ g/day); Group III did not receive FM or PGF\( F_{2a} \). Mean concentrations of PGFM were lower in group...} \end{quote}
FIGURE 1. Profile of least squares daily means of 15-keto-13, 14-dihydro-PGF\textsubscript{2a} (PGFM) concentrations from day 2 postpartum to day 15 postpartum in Holstein heifers bred to either Holstein, Brahman or Angus bulls.

I (FM + Saline; 611 < 1058 pg/ml) than group II (FM + PGF\textsubscript{2α}) and postpartum profiles (Figure 3) of groups I and II differed from group III (control). Postpartum decreases in uterine horn diameters of previous gravid and nongravid horns were similar among groups and were completed by day 35 postpartum. Although postpartum concentrations of PGFM were reduced in Group II (FM + Saline), uterine (uterine horn diameter and location of the uterus) and cervical (cervical diameter) involution were not affected by partial suppression of endogenous prostaglandins during the early postpartum periods. Physiological processes involved in uterine involution such as vasoconstriction, peristaltic muscular contractions, and re-organization of connective tissue framework could be initiated despite a significant reduction in prostaglandin production during the early postpartum period. Although a basal endogenous production of prostaglandins does not appear to be an obligatory factor in the process of uterine involution, an augmentation of PGF\textsubscript{2α} secretion may enhance the processes of uterine involution. Both higher magnitudes\textsuperscript{27,29,30} (Figure 1) and longer duration\textsuperscript{32,33} of the endogenous release of PGF\textsubscript{2α} from the uterus, as assessed by measurement of peripheral plasma PGFM concentrations, were related to faster involution of the uterus.

Swedish workers\textsuperscript{32,33} related the duration (days) of elevated PGFM concentrations postpartum with the time required for completion of uterine involution. In essence, animals without clinical signs of reproductive disorders showed a trend where the longer durations of increased prostaglandin metabolite concentrations also had the shortest times of uterine involution (32, R\textsuperscript{2}=.25; 33, R\textsuperscript{2}=.17). It was found that animals with abnormal vaginal discharge had a tendency for an opposite relationship (i.e. long duration of prostaglandin release and longer involution time). The dynamics of uterine prostaglandin secretion as related to uterine health (normal, abnormal, bacterial flora and toxins) warrants further investigation.

A recent report\textsuperscript{34} characterized the periparturient changes in PGFM concentrations of Holstein cows with (RFM; n=10) or without (NRFM; n=12) retained fetal membranes. Increases in mean peripheral concentrations of PGFM were evident in RFM cows 6 days before parturition as compared to 48 hours before parturition in the NRFM group. A gradual decline in the PGFM levels to prepartum concentrations occurred in both groups by day 12 postpartum; although higher values were present in the RFM cows on days 1, 3 and 18 after parturition. It would appear that cows destined to have retained fetal membranes have an earlier activation of prostaglandin production within the uterus and conceptus (fetus, fetal fluids and placentome), and that retention of fetal membranes may
enlarge amount of necrotic material postpartum and contribute to a higher prostaglandin secretion. The latter observation is interesting since RFM cows had a comparable period of uterine involution and cows with retained fetal membranes have a greater rate of uterine contractions.

References

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