Physiology and Pharmacology of the Postpartum Cow and Retained Fetal Membranes

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Retained fetal membranes (RFM) in dairy cows are frequently associated with postpartum endometritis, delayed involution, delayed onset of cyclicity, and reduced reproductive performance. Numerous reports and recommendations for the treatment of RFM have been published, yet the search continues for a method to prevent the occurrence of the condition or at least reduce its effect on fertility.

Endocrinology

A number of studies have been reported in which endocrine profiles of cows either retaining or not retaining their fetal membranes were determined. A higher prepartum concentration of progesterone and both higher and lower levels of estrogens have been reported in cows with RFM (1-4). Although the comparisons with normal cows varied, most authors agreed that it was not necessarily the absolute values of these hormones that were important, but the ratios of progesterone to estrogen in relation to the time of calving. More recent studies have not clarified the issue. Heuwieser and Grunert have reported that progesterone did not vary between cows with or without RFM although total estrogens were lower in cows with RFM (5). Peter and Bosu also did not find a difference in progesterone in cows with or without RFM (6). At this point it would be difficult to prevent RFM by endocrine therapy because the causal relationship is not clear.

Several workers have also looked for an association between corticosteroids and RFM. Earlier work did not find a difference between RFM and nonRFM cows in this regard (7). However, a recent study by Peter and Bosu showed that starting day 6 prepartum, cows that had RFM had elevated cortisol concentrations compared to normal cows (6).

Concentrations of prostaglandin (PFG) or its metabolite (PGFM) have been reported in postpartum cows as well as in prepartum cows that subsequently had RFM. In normal postpartum cows, PGF peaks within a few days after parturition and declines gradually to a baseline level by 15-20 days postpartum. Normal cows with a slower decline to baseline experience more rapid uterine involution and an earlier return of ovarian activity (8). However, cows with an abnormal puerperium also experience prolonged PGF release postpartum.

The association of prolonged PGF release with more rapid uterine involution has resulted in an interest in the pharmacological applications of PGF for uterine motility and involution. Three cows that were administered 25 mg of PGF twice daily from days 3-13 postpartum were reported to involute approximately one week sooner than untreated controls (9). In contrast, Gustafsson reported that suppression of endogenous PGF by administration of the prostaglandin synthetase inhibitor flunixin meglumine (2.2 mg/kg twice daily on postpartum days 1 to 10) resulted in more rapid uterine involution in treated cows (10). Another study showed that administration of flunixin meglumine to postpartum cows on days 1 to 10 after calving did not inhibit uterine involution although it did seem to negatively affect the resumption of ovarian activity (11). There is no good evidence at this time to support the use of PGF for acceleration of postpartum uterine involution.

Peter and Bosu recently reported that significant increases in PGFM concentrations occurred in RFM cows between days 7 and 6 prepartum compared with normal cows (6). This, together with the finding of increased cortisol values in these cows, suggested that the events resulting in RFM began at least one week prior to parturition. Since the source of PGF at this time has been determined to be the uterus (12), the possibility of uterine/placental inflammation as a cause of RFM must be considered.

Prostaglandins clearly have uterotonic effects and have been used in attempts to evacuate RFM and uterine contents during the early postpartum period. Prostaglandin analogues with longer half lives have been shown to stimulate uterine motility in estradiol-primed ovariectomized nonpregnant cows longer than PGF (fenprostalene, 19 hours; cloprostenol, 8.9 hours; dinoprost, 7.7 hours) (13). One well publicized study with fenprostalene in cows with RFM showed more rapid expulsion of the fetal membranes (60 vs 98 hours) and a lower prevalence of metritis (41 vs 75%) than in cows with RFM that received "conventional treatments" (14). A subsequent study was not able to confirm this benefit (15). It is questionable whether PGF should be expected to cause expulsion of RFM due to stimulation of myometrial contractions because cows with RFM have as much uterine motility as normal cows (16, 17).

An interesting study recently reported that cows induced to calve with dexamethasone 5 days prior to their due date had a markedly reduced rate of RFM (8.8 vs 90.5%) if they received 10 mg of PGF within one hour postcalving (18). The same research group had also reported that fetal placental villi from cows that would subsequently retain the fetal membranes produced prostaglandins primarily of the E series

(PGE). This was in contrast to fetal villi from placentas that would be dropped normally, which produced primarily PGF. They hypothesized a failure of fetal placental villi to shift in late gestation from PGE to PGF production in placentas that would be retained. This seems to contradict the findings of Peter and Bosu, that cows which were destined to retain the fetal membranes had higher circulating, and therefore presumably placental/uterine, production of PGF (6).

We have tried to repeat the findings of Gross *et al.* at Texas A&M with beef cattle. Prostaglandin (25 mg) was administered within one hour of calving to cows induced to calve 10 days early with dexamethasone or prostaglandin. This did not reduce the incidence of RFM in these cows over those induced and receiving saline (over 80% of both groups of cows induced had RFM vs 8% of noninduced controls). Perhaps the earlier induction (10 days prior to the due date vs 5 days in the other study) influenced the results (19). More work in this area is needed.

After calving, gonadotropin releasing hormone (GnRH) is secreted infrequently in small quantities (20). Follicle stimulating hormone (FSH) concentrations, which are low during the last 10 days prepartum, increase within 5 days postpartum to near the level at which they will remain until at least day 30. Follicular development is stimulated at this time. If follicles of sufficient size (>15 mm) are present, GnRH induced LH surges can induce ovulations prior to day 20 (21).

Luteinizing hormone (LH) concentrations increase slowly, until day 20 postpartum. Pituitary release of LH in response to GnRH is reduced at parturition, with responsiveness returning by approximately day 10. There is an increase in the frequency of the pulsatile pattern of LH prior to ovulation. The greater the frequency of LH pulses between days 10 and 17 postpartum, the shorter the time to the onset of ovarian cyclicity.

Developing follicles secrete estradiol, which normally has a positive feedback effect on LH prior to ovulation. The positive feedback is absent at parturition but is restored by day 15 postpartum at which time ovarian cycles can resume. Ovarian follicles also secrete inhibin and other substances which modify FSH secretion and further follicular development.

Cows in which ovarian cycles are delayed may have persistently low levels of gonadotropins. This may be associated with an abnormal sensitivity to feedback mechanisms, increased corticosteroid concentrations, abnormal concentrations of PGF, or inhibition of GnRH release by endogenous opioid peptides (20,22). It has been reported that PGF levels return to baseline before the first postpartum ovulation, suggesting an inhibition of cyclicity by this compound. However, injections of cloprostenol have been reported to shorten the time to onset of cyclicity and administration of a prostaglandin synthetase inhibitor partially suppressed postpartum ovarian activity (11, 20). Endogenous opioids have been found to interact with gonadal steroids and adrenergic compounds in the control of GnRH, and therefore, LH release. Administration of naloxone, an opioid antagonist, has been associated with increased LH secretion in several species (22).

The majority of cows with endometritis spontaneously clear the disease once cyclicity resumes postpartum. Therefore, early resumption (induction) of cyclicity is desirable. GnRH and PGF have both been used pharmacologically to manipulate postpartum estrous cycles in cattle. GnRH has the potential to induce ovulations in postpartum cows that have follicles large enough to respond. Prostaglandins theoretically should only work to induce estrus in cows that have already ovulated. However, reports are available that suggest a benefit of treatment in some cows that appear not to be cycling. Perhaps PGF induces gonadotropin release in the cow, as has been reported in the bull (20). Although not currently feasible, the use of opioid antagonists to induce ovulation may someday become a reality.

The use of PGF and/or GnRH in the treatment of postpartum endometritis has recently been reviewed (23). Results vary between herds to the extent that each situation must be evaluated independantly. As an example, one study reported that the administration of 200 ug GnRH once between days 10 and 14 postpartum or the administration of 25 mg PGF once between days 20 and 24 reduced days open by 43 to 48 in dairy cows with an abnormal puerperium or by 27 to 29 when normal and abnormal cows were considered together (24). Other studies have been equivocal, suggesting benefits of GnRH treatment only in cows with abnormal puerperia or in herds that begin breeding cows prior to 80 days postpartum. Cows that have uterine infections when they are induced to ovulate may be at an increased risk of pyometra, and so should be monitored. One way would be to use progesterone tests to determine when the cow becomes eligible for PGF treatment for induction of estrus.

Uterine Defense Mechanism

An area that has received increasing attention in recent years is that of the innate defense mechanisms of the genital tract. This includes a number of diverse areas concerning the ability of the uterus to combat infections whether by killing bacteria or by physically removing them along with remaining uterine contents.

Uterine blood flow. This consideration is of interest because the blood supply contains phagocytic blood cells as well as other components of the immune system. It also delivers any antimicrobial drugs that have been administered systemically.

Uterine blood flow is generally considered to be increased in association with estradiol elevations (25). This has typically been investigated in nonpregnant cows with involuted uteri. The response of uterine vasculature to estradiol, however, may be mediated by adrenergic receptors. Vascular smooth muscle contains alpha-adrenergic (vasoconstricting) and beta2 (vasodilating) receptors. Uterine vasculature has been shown to be dominated by alpha-receptor activity although beta receptors can also modulate uterine blood flow (25). Therefore the potential exists, at least in estrogen-

primed animals, to increase uterine blood flow by selectively blocking alpha receptors or stimulating beta2 receptors. Whether this effect could be achieved in the early postpartum uterus needs to be studied. There is a marked reduction in uterine blood flow (26) as well as estradiol levels at or soon after the time of calving, associated with termination of the blood supply to the fetoplacental unit. When or if it would be desirable to pharmacologically modify the uterine blood supply after calving has not been determined.

Uterine motility/contractility. The ability to pharmacologically influence the evacuation of uterine contents has been investigated. The use of prostaglandins has been previously discussed. They do cause uterine contractions but clinically their benefit is often not discernible, possibly because lack of uterine motility is often not the problem.

Oxytocin has been used clinically for many years to promote contractility of the postpartum uterus. Estrogen priming of the uterus is generally considered to be necessary, because as estrogen levels decrease after parturition, oxytocin becomes less effective. Burton *et al.* used strain gauge transducers to study the effect of different doses (2, 5, 10, 20, 40 USP) and days postpartum on uterine response to oxytocin (27). All doses increased contraction frequency through day 6 postpartum, with the magnitude of the increase being dependant on dose and day postpartum. Tubo-cervical wave propagation was observed at all doses used. The last detectable response to 2, 5, 10, 20, and 40 USP was seen on postpartum days 6, 7, 8, 9 and 10 respectively. Duration of response with 20 or 40 USP was longer (approximately 140 minutes) than at the lower doses, and declined with days postpartum. A 6 to 10 minute spasm occurred after administration of 40 USP suggesting that the optimal dose was between 20 and 40 USP.

Long-acting analogues of oxytocin may provide benefit because of the short half-life of the parent drug. Mean uterine response duration of one such analoque was reported to be between approximately 7 and 10 hours, compared to 2.5 to 3 hours for oxytocin (28).

Estrogen has also been used in an attempt to mimic the tonus observed during estrus. Other hoped for effects include increased mucus secretion, increased blood flow, and increased resistance to infection. Exogenous estrogen (15 mg estradiol cypionate (ECP) daily for 3 days) was shown to improve the phagocytic capabilities of uterine leukocytes collected from ovariectomized cows (29). However, the use of pharmacological doses of estrogen in the postpartum cow has not been demonstrated to be beneficial. Burton *et al.* studied the effects of ECP on myometrial contractility and found that estrogen caused a tetanic-like spasm of the myometrium rather than the spontaneous tubo-cervical propagation of contractions (30).

Uterine smooth muscle contains adrenergic receptors. Stimulation of beta2 receptors causes relaxation and stimulation of alpha1 receptors causes contraction (31). Beta2 receptor antagonists have been tried clinically to assist in expulsion of fetal membranes, but without significant benefit (32). Beta agonists have been used with some success in postponing parturition. If more selective and potent drugs are developed, this type of treatment might be of use in the future.

It was reported several years ago that stress associated with a painful or otherwise abnormal parturition might result in RFM due to release of adrenalin, stimulation of b2 receptors, and the consequent inhibition of uterine motility (33). Another possibility was the inhibition of oxytocin release due to stress related production of endogenous opioids. The author had used the endorphin antagonist naloxone in postpartum cows with uterine atony with subsequent induction of strong uterine contractions. However, again, lack of uterine motility is not common in cows with RFM.

Immunology. Some of the recent studies on RFM have focused on events at the cellular level. The *in vitro* chemotactic activity of placentomes from animals with or without RFM have been compared using leukocytes (PMN) from the blood of cows with or without RFM. The assay involves the use of cotyledon suspensions and peripheral blood leukocytes in a Boyden Chamber. The leukocytes and cotyledon suspension are separated by a polycarbonate membrane with a pore size such that leukocytes can only pass through it actively, i.e. if the substance on the other side has a positive chemotactic effect. After incubation, the membrane is placed on a slide and the leukocytes counted. Higher numbers of cells are supposed to be associated with higher chemotactic properties of the suspension.

Gunnink has reported a series of experiments using this technique. First, he reported that cotyledons with a positive chemotactic effect came from cows that had only a 2.6% incidence of RFM while cotyledons with a negative chemotactic effect came from cows with a 35.6% incidence of RFM (34). Next, he found that during the immediate prepartum period, peripheral leukocytes of cows without RFM were active against cotyledons from other nonRFM cows but not against cotyledons from RFM cows (35). This confirmed that cotyledonary tissue from normal cows contains some chemotactic substance that similar tissue from cows destined to retain the fetal membranes does not, and that this difference appears at least one week prior to parturition. Another finding of interest was that peripheral leukocytes from cows with RFM were not attracted by cotyledons from RFM or nonRFM cows. This suggested a decreased function of leukocytes in cows with RFM (36). The decreased function was demonstrated in the postpartum period as well. Because dilution of cotyledon suspensions from RFM cows resulted in increased chemotactic activity for leukocytes, Gunnink proposed the presence of a chemotaxis inhibiting factor in cotyledons from cows with RFM (37).

Heuwieser and Grunert have extended these findings and correlated them with stressful conditions occurring at the time of calving (38). They used 3 groups of cows, one of which was hospitalized prior to parturition, one which was transported to the hospital on the day of parturition (stress) and did not have RFM, and one which was transported (stress)

and subsequently had RFM. Leukocytes from cows that were transported but without RFM had reduced chemotactic activity immediately after parturition compared to the hospitalized cows but had similar activity by 3 hours postpartum. Leukocytes from cows that were transported and had RFM had markedly reduced activity at parturition as well as 3 hours later. Therefore it seems that low chemotactic activity of placental tissue as well as inhibited migratory ability of leukocytes may be part of the RFM syndrome and that stress may influence these parameters.

One important aspect of uterine resistance to bacteria is the opsonising capacity of uterine secretions. This has received much attention in mares but less in cattle. Watson reported a technique for obtaining uterine neutrophils by infusing the uterus with oyster glycogen (39). The neutrophils were used in an *in vitro* bactericidal assay with *Staphylococcus aureus.* Incubation of either blood or uterine neutrophils with uterine flushings from follicular phase cows resulted in increased bactericidal activity compared to incubation with flushings from luteal phase cows. This suggests that plasma infusions might be of benefit in certain cows with chronic endometritis, as has been reported in mares (40). More information on this technique and other aspects of the bovine uterine defense mechanism is needed.

Pharmacology

Hormones. The use of some of the currently available hormones has already been discussed. Another hormone with potential uses is progesterone (progestins). Commercially available progestins (norgestomet) are not approved for use in lactating dairy cows. They would potentially be of benefit in postpartum anestrus, because their application and removal could result in ovulation in some noncyclic cows.

Antimicrobial drugs. Cows should be carefully selected for antimicrobial therapy. Therapy should take into consideration the causative organisms, the sensitivity patterns of these organisms, the interaction of the drugs with the uterine environment, and the pharmacokinetic behavior of these drugs in the genital tract. These aspects of therapy have been recently reviewed (23, 41).

The lumen of the early postpartum bovine uterus is an anaerobic environment frequently containing a variety of microorganisms, fluid, and tissue debris. The tetracyclines are currently in favor for intrauterine (IU) treatment of the postpartum uterus because they are broad spectrum, effective in the presence of pus, and effective under conditions of reduced oxygen tension (42). Intrauterine administration of these or other drugs result in high concentrations in the uterine lumen and surface of the endometrium. For example, 24 hours after IU infusion of 5.5 mg oxytetracycline/kg to postpartum cows with metritis, mean concentrations of the drug were 42 ug/g in caruncles, 25 ug/g in endometrium, but only 0.57 ug/g in the uterine wall (23). These extremely high local concentrations may help overcome the demonstrated negative effect of uterine lochia on the minimal bactericidal concentrations (MBC) of several antimicrobials (43). In *in vitro* tests, pasteurized uterine secretions increased the MBC of penicillin G, ampicillin, and oxytetracycline by 4- to 64-fold. This lends validity to the recommended practice of flushing the uterus of cows with toxic metritis prior to IU antimicrobial treatment although the risks of this procedure must be realized (44).

Relatively high doses of systemically administered antimicrobials may be necessary to achieve therapeutic concentrations in the early postpartum uterus (23, 41). Plasma to uterine tissue ratios of oxytetracycline at steady state equilibrium were 1.08 in cyclic cows but 1.36 in postpartum cows. Systemic administration is necessary to achieve therapeutic concentrations in genital tract tissue other than the endometrium. Systemic penicillin (5-10,000 I.U./kg twice daily) has been recommended for cows with clinical signs of illness due to uterine infection because of the likelihood of involvement of Clostridial organisms at this time (42).

In the chronically infected uterus, *Corynebacterium pyogenes,* possibly with a Gram negative anaerobe, is likely to be cultured. Induction of estrus with PGF is indicated if a corpus luteum is present. Otherwise IU application of one million I.U. of penicillin has been recommended. Multiple treatments are advisable because the bacterial populations may have entered a lag phase and not be actively dividing. Penicillin requires cellular division for its antimicrobial activity.

Penicillin is not recommended for IU application during the early postpartum period because the microflora at this time probably includes penicillinase producers. Aminoglycosides are not recommended for IU use in the postpartum uterus because they are ineffective in an anaerobic environment. Sulfonamides are not recommended for postpartum IU use because they are generally ineffective in the presence of cellular debris (42).

One report indicated that IU application of tetracycline every other day to cows with RFM until one treatment after the membranes were expelled resulted in fertility equal to that of normal herdmates (45). Yet others report that despite rather aggressive therapy of RFM cows, a significant incidence of endometritis remains. DeBois stated that "despite repeated IU treatments with antibiotics, effective infection therapy could be achieved only in a small number of cows within a period of 3 weeks postpartum. These results do not favor the use of antibiotics as repeated intrauterine treatments and are both time consuming and expensive" (46). A single treatment may be sufficient although these cows are at risk of a prolonged infection and should be monitored.

The effects of IU treatment on the uterine defense mechanism should not be overlooked (47). Cows with an abnormal puerperium (dystocia, RFM, metritis) already have decreased phagocytic activity by uterine leukocytes. Most antiseptics and many antimicrobials, as well as uterine manipulations, depress phagocytosis as well. Therefore, antimicrobial therapy may be less effective than expected

because ineffective host defenses allow bacterial growth and inflammation to resume as soon as concentrations of the drug decline.

The use of irritating IU products should be discouraged. The fertility of rats infused with tincture of iodine was depressed for 3 to 4 weeks after histological resolution of the necrotizing endometritis (48). Whether a similar "carry over" effect of endometrial necrosis occurs in cattle needs to be investigated.

A potential consequence of IU application of antimicrobials is the occurrence of residues. The uterus, especially the early postpartum uterus, is a less efficient site of absorption of antimicrobials than is muscle. However, absorption of even small doses of IU antimicrobials does occur (23). Miller and Bergt recommended a withholding time of 24 hours after IU administration of 4 mg/kg oxytetracycline (49). Manners and Stewart recommended 72 hours withholding after IU application of 1.5 g procaine penicillin (50). Messer *et al.* suggested a 24 hour withholding after IU infusion of 4000 I.U./kg penicillin (51). McClary reported that most cows receiving 1-2 million I.U. potassium penicillin G had cleared milk residues by 24 hours although one cow had detectable concentrations as long as 60 hours postinfusion (52). Using the *Bacillus stearothermophilus* disk assay, Haaland *et al.* reported residues in milk for 72-84 hours after 3 g of oxytetracycline IU; for 60 hours after 500 mg of oxytetracycline; for 72-84 hours after 3 daily infusions of 500 mg of oxytetracycline; for 60-84 hours after infusion of 1.5 million I.U. of procaine penicillin G; and for 48-72 hours after infusion of 1 g of ampicillin trihydrate (53). Kaneene *et al.* reported that approximately half of 61 cows infused with 3 g of oxytetracycline had milk residues for times ranging from 12 to 44 hours (54). They also reported that severity of metritis did not influence retention time, but retention time decreased as the postpartum interval increased.

In order to avoid the consideration of milk withholding, a variety of antiseptics, including chlorhexidine and dilute iodine have been used. These compounds should still be used judiciously, especially iodine preparations, some of which can be extremely irritating. In most cases, their efficacy remains to be demonstrated.

Therapy of genital tract infections in the future will probably center less on the use of antimicrobials and more on stimulation or manipulation of innate uterine defense mechanisms. Hormonal treatments to induce uterine motility, increase blood flow, and enhance leukocytic function may become commonplace.

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