Metritis/Endometritis: Medically Sound Treatments

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Bacteriology of the Postpartum Uterus

If antimicrobials are to be used effectively for the treatment of metritis/endometritis, it is important to understand the bacteriology of the postpartum uterus. A wide variety of bacterial species have been isolated from the postpartum uterus. These isolates include gram-positive and negative bacteria that have aerobic to fastidious anaerobic requirements. Isolation of fastidious obligate anaerobes from the postpartum uterus provides supporting evidence that the postpartum uterus is an anaerobic environment. Presence of fastidious anaerobic bacteria implies that antimicrobials should be selected that are active in an anaerobic environment. The bacterial species, frequency of isolation, and relative concentration of bacteria species change with time through the postpartum period. Most species of bacteria isolated from the uterus have little significance with the exception of clostridium, *Actinomyces pyogenes,* and gram-negative anaerobes. *A. pyogenes* and gram-negative anaerobes are components of metritis in the early postpartum period as well as the primary cause of severe endometritis in the middle and late postparturm period. Clostridial organisms are frequently a component of severe postpartum metritis. Hartigan, *et al.*, 1974, observed that intrauterine infections with *A. pyogenes* invariably induced endometritis. Severity of the endometrial inflammation was determined by the duration of the infection and whenever the infection persisted for more than a week, severe endometritis developed. Gram-negative anaerobes like *Fusobacterium necrophrum* and *Bacteroides* spp act synergistically with *A. pyogenes,* resulting in a more severe endometrial pathology than with *A. pyogenes* alone.

Diagnosis of Endometritis

Although uterine cultures can be used to confirm the presence of infections with *A. pyogenes,* they are expensive and have significant time requirements before results are known. Hence, uterine cultures are rarely used in clinical practice. Rectal palpation, although the most frequently used method of diagnosing endometritis, has a weak correlation with uterine culture and biopsy. Vaginal speculum examination for the identification of purulent discharge at the external os of the cervix or in the vagina is a more accurate method of identifying uterine infections than rectal palpation. Miller *et al.*, 1980, found that 59% of the cows classified as infected by speculum examination had positive uterine cultures compared to 22% of the cows classified as positive by rectal palpation. Stevens, *et al.*, 1995, compared the results of uterine cultures from cows in which the uterine lumen was palpable per rectum (PUL) to cultures from normal herdmates taken between 28 and 42 days postpartum. The incidence of isolation of aerobic and/or facultative anaerobic bacteria from cows with PUL (14/15) was not different from normal cows (13/15). Anaerobic bacteria were isolated from 1 cow with PUL. On the basis of histological classification, 11 of 15 normal cows had normal to mild endometrial changes. In contrast, only 6 of 15 cows with PUL had normal to mild endometrial changes while 9 cows had moderate to severe endometritis. The results of the study re-emphasize the inaccuracy of rectal palpation in determining infection status and histological status of inflammation in the uterus. Part of the problem in using rectal palpation to identify uterine infections is that inflammation which is the result of infections may persist for a period of time following the clearance of *Actinomyces pyogenes* from the uterus. Although there may be inflammation of the uterus, there is little or no benefit from antibiotic therapy if the cow's defense mechanisms have resolved the infection.

Antimicrobial Treatment of Metritis/Endometritis

Uterine Environment

Factors to consider in the selection of antimicrobials for the treatment of endometritis are the uterine

environment, the pathogen, the MIC of the pathogen, route of administration of the antimicrobial, the severity of irritation caused by the antimicrobial agent or vehicle to the endometrium used for intrauterine therapy, the economics of treatment, and the outcome of therapy. The uterine environment has several features which affect selection of antimicrobials. Isolation of fastidious anaerobic bacteria from the postpartum uterus indicates that the postpartum uterus is an anaerobic environment. Certain antibiotics such as the aminoglycosides are not effective in an anaerobic environment of the uterus. The postpartum uterus has varying amounts of lochia. Uterine lochia is an alternative source of metabolites for bacteria which reduces the effectiveness of antimicrobials such as sulfamides which act by blocking metabolic pathways. In addition to supplying metabolites, lochia may reduce the effectiveness of antimicrobials by other mechanisms. Pasteurized uterine secretions have increased the minimal bactericidal concentrations for penicillin, ampicillin, and oxytetracycline 4 to 64 times the minimal bactericidal concentration in nutrient both. The bacterial population of the uterine environment changes from a fairly diverse population in the early postpartum period to a select population of *A. pyogenes* and gram-negative bacteria toward the end of the first month postpartum in cows with endometritis.

Effect of Infusion of Irritants on the Postpartum Uterus

Although compounds as irritating as Lugol's iodine have been infused into the uterus, there are few studies that have evaluated the effect of irritant infusions on subsequent fertility. Nako, *et al.*, 1988, studied the effect of routine postpartum intrauterine infusion of 2% polyvinylpyrrolidone (PVP)-iodine solution, a mild irritant, on the reproductive performance of randomly selected dairy cows at 35 days postpartum. Although the routine postpartum infusion did not benefit the reproductive performance of treated vs non-treated herdmates, the intrauterine infusion of PVP-iodine solution was detrimental to the fertility of cows with endometritis. The implication of this study is that the infusion of irritants into the uterus of cows with a healthy endometrium may not have an adverse effect on fertility but the infusion of irritants into the uterus of cows with diseased endometrium may adversely affect fertility. Not only do antimicrobials vary in the degree of irritation to the endometrium but the vehicles used to carry the antimicrobials may vary in the severity of irritation. Oxytetracycline (OTC) in a propylene glycol base is more irritating to the endometrium than OTC in a PVP base. The form of the antibiotic may vary in the severity of irritation. While OTC in a PVP vehicle causes mild irritation when infused in the uterus, OTC powder dissolved in extracellular replacement fluid and infused in the uterus cause a coagulation necrosis of the endometrium and severe inflammation. Damage to the endometrium may have a "carry over" effect on fertility. Dafalla, *et al.*, 1983, observed that a deleterious effect on fertility persisted 3 to 4 weeks after resolution of a necrotizing endometritis induced by infusion of tincture of iodine in rats. There is little evidence to suggest that the infusion of irritants improves reproductive performance and some evidence that irritants adversely affect fertility, particularly in cows with endometritis.

Selection of Anitimicrobials for Parenteral Therapy

The bacteria primarily responsible for a febrile response and systemic signs associated with puerperal metritis are *A. pyogenes,* gram-negative anaerobes, and frequently clostridial organisms. Procaine penicillin G, ampicillin, and amoxicillin seem to be appropriate selections for parenteral therapy.

Selection of Antimicrobials for Intrauterine Infusion

The ideal antimicrobial for intrauterine therapy in the early postpartum period would be active in an anaerobic environment, would not be inhibited by lochia, would not be irritating, and would have broad spectrum activity. The tetracyclines most closely meet these criteria for an intrauterine antimicrobial in the early postpartum period. Cohen, *et al.*, 1995, determined the minimum inhibitory concentration (MIC) of OTC for *A. pyogenes* isolated from the uterus cows with retained fetal membranes and post-parturient endometritis. The MIC of OTC for 90% of the *A. pyogenes* isolates was >100 ug/ml. The majority of *A. pyogenes* isolates recovered from the uterus of cows in this study were resistant to OTC. The relevance of the finding from this study raise questions on the value of OTC in the treatment of endometritis.

Results of Trials with Intrauterine Infusion of Antimicrobials

For as commonly as retained fetal membranes and endometritis occur in dairy cows, there is a lack of controlled trials to evaluate effectiveness of intrauterine therapy. Dawson, *et al.*, 1988, evaluated the effect of intrauterine infusion of OTC on reproductive performance of 20 cows with retained fetal membranes and 47 cows with postpartum metritis in comparison to 47 normal non-treated postpartum cows. The reproductive

performance of the cows treated with OTC was excellent and comparable to normal, untreated postpartum cows. However, the study did not have non-treated cows with metritis or retained fetal membranes to compare with the treated cows. Thurmond, *et al.*, 1993, conducted a trial evaluating the effect of a single intrauterine infusion with procaine penicillin G or OTC in cows with endometritis, on reproductive performance. Cows were examined about 21 days post-calving in one herd and 10 to 15 days in the other herd and a diagnosis was based on the presence of an abnormal discharge. There was no significant difference in the cumulative proportion of cows remaining nonpregnant between the treated and non-treated cows with endometritis with either OTC or penicillin intrauterine infusions. The difference in the cumulative proportion of normal cows that were pregnant was greater than cows with endometritis in one herd but not in a second herd. A trial by Callahan and Horstman, 1993, compared the treatment of cows with metritis with intrauterine infusion of OTC or systemic prostaglandin (PGF) to untreated control cows. Nine cows in the OTC group received 3 gm OTC for 3 consecutive days, six cows were treated with PGF on 3 consecutive days, and six cows were left untreated. Twenty-one of 24 cows diagnosed with metritis by rectal palpation were positive for *A. pyogenes* and included in the trial. At a second examination 14 days after initial diagnosis, cows were examined and samples taken for culture. None of 9 OTC cows, 4 of 6 PGF cows, and 2 of 6 control cows had purulent or mucopurulent vaginal discharge. Results of the second uterine culture showed 1 of 9 OTC cows, 4 of 6 PGF cows, and 4 of 6 control cows were positive for *A. pyogenes*. There was a significant reduction in the number of cows infected with *A. pyogenes* in the OTC group compared to the PGF and control group. However, the question that remains is whether the treatment significantly altered the course of resolution of the inflammation and subsequent fertility.

Conclusion

Intrauterine infusion of OTC with uteri infected with *A. pyogenes* can reduce the rate of infections compared to untreated controls. However, the outcome of intrauterine infusion is affected by several factors. The accuracy of identifying cows with active uterine infections with *A. pyogenes* by rectal palpation is poor. This makes it difficult to evaluate the effectiveness of intrauterine therapy. Cows with inflammation of the uterus following infection with *A. pyogenes* may have cleared the infection at the time of rectal examination. If cows have had an infection with *A. pyogenes* for more than a week at the time of treatment, they will likely have a severe endometritis at the time of intrauterine infusion and fertility will be less than non-infected herdmates even if the infusion successfully eliminates the infection. The normal propensity of the cow with a uterine infection associated with *A. pyogenes* is for the cow to clear the uterus of the infection. All this makes it extremely difficult to evaluate intrauterine therapy.

Postpartum Hormonal Treatment of Dairy Cows

There is increased interest among veterinarians and dairy producers in finding effective hormonal therapies for uterine infections in dairy cattle. Tests for detecting antibiotic residues in milk have become increasingly more sensitive and have raised concerns among producers and veterinarians that extra-label use of antibiotics for treatment of uterine infections may lead to violative antibiotic residues in bulk tank milk or in the carcass of cows sent to slaughter following therapy of individual cows.

Use of Luteolytic Prostaglandins in the Postpartum Cow

Luteolytic prostaglandins, either prostaglandin 2-alpha or its analogues (PGF), have been used in many trials to evaluate their potential value as a treatment for endometritis and/or for improving the reproductive performance of dairy cows when treated within the first 40 days of the postpartum period. Three types of trials give insight into the value of postpartum PGF injections as a treatment for endometritis and as a profertility agent to improve reproductive performance in dairy herds: 1) Whole herd trials in which cows were randomly assigned regardless of peripartum disease status for comparison of cows treated with PGF in the postpartum period to non-treated herdmates, 2) Trials in which cows were selected because they were considered to be at high risk for uterine infections resulting from postpartum diseases such as retained fetal membranes or dystocia and were assigned to postpartum PGF therapy or non-treated herdmates for comparison of reproductive traits, and 3) Trials in which cows were selected that had a normal peripartum to evaluate the comparative benefits of postpartum PGF treatment on reproductive performance. The results from the 3 types of trials are shown in Table 1. There is little difference in days open between treated and untreated herdmates in the trials using cows from the whole herd or cows with normal peripartums. However, when the days open are compared between treated and untreated cows in trials using cows with abnormal peripartums, there is a slight, nonsignificant reduction of 5.3 days open for the treated cows. When the differences in average days open were examined by the three categories of trials, only routine treatment of cows with abnormal peripartums seems to have the potential of being economically justifiable.

Table 1. Weighted Averages of Days Open for Untreated and PGF Treated Cows by Category of Trial.

	No. of Studies	PGF Group		Ctrl Group		Ctrl Minus PGF
		Days Open	No of Cows	Days Open	No of Cows	
Whole Herd Trails	13	92.9	1690	94.4	1625	1.5
Abnormal Peripartum Trials	8	112.7	532	118.0	450	5.3
Normal Peripartum Trials	4	89.7	392	87.7	415	-2.0

Using average days open to evaluate the benefits of routine treatment of cows with PGF in the postpartum period may not be the most effective method for determining response. When the change in days open for cows treated with PGF in the postpartum period is graphed against the days open for untreated herdmates by trial or herd, there appears to be an increasing advantage for treating cows with PGF as the days open increases for the herd (Figure 1). By plotting the change in days open for studies in which cows were treated with PGF against the days open for untreated herdmates in all trials, the graph shows that herds with long days open appear to benefit the most from routine treatment of postpartum cows with PGF. When a comparison was made of the effect of PGF treatment in the studies with days open for control cows was less than 100 days to studies in which days open was greater than 100 days, there was no advantage to postpartum PGF therapy. However, when a comparison was made of PGF treated cows for studies in which days open for untreated control cows was greater than 100 days, there was a significant reduction of days open in the PGF treated cows (Table 2). Selection of herds for routine postpartum PGF therapy should begin by evaluating days open for the herd and selecting potential herds with days open greater than 100 days.

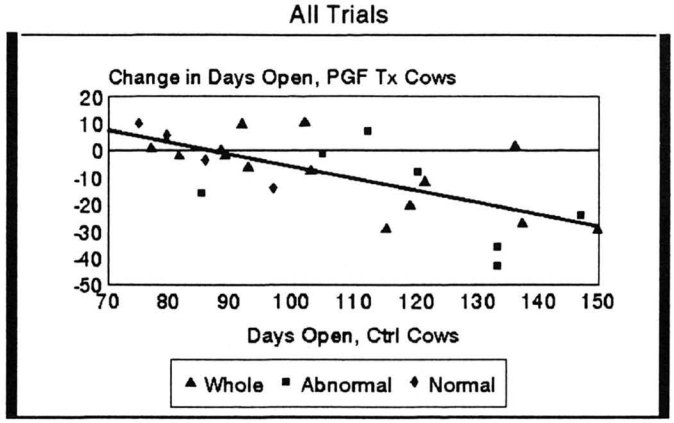

Figure 1. Effect of PGF on change in Days Open.

Table 2. Comparison of Effect of PGF Treatment on Days Open for Studies with Days Open Above or Below Mean of 22 Studies.

	Ave of Studies with Days Open < 100	Ave of Studies with Days Open > 100	Average of All Studies
Ctrl	85.4	116.7[a]	101.0
PGF	85.6	109.1[b]	97.4
Difference	-0.2	7.6	3.6

ab, $P < 0.06$

Days open for herds using artificial insemination is controlled by three factors; days in milk at first breeding, efficiency of heat detection, and herd fertility as measured by conception rate. If days open for the herd is to be reduced, one or more of these control factors must improve. If days open are reduced following PGF treatment of postpartum cows, it seems that an improvement in first service conception rate is the most likely source. Overall, there was remarkably little difference in the average first service conception rate between cows treated with PGF and untreated herdmates whether the comparison is made on a whole herd basis, cows with abnormal peripartums, or cows with normal peripartums. However, when the change in first service conception rate of cows treated with PGF in the postpartum period is graphed against the first service conception rate of untreated herdmates, the primary advantage of postpartum PGF treatment appears to occur in herds with a first service conception rate below the average first service conception rate of all cows in whole herd trials (Figure 2).

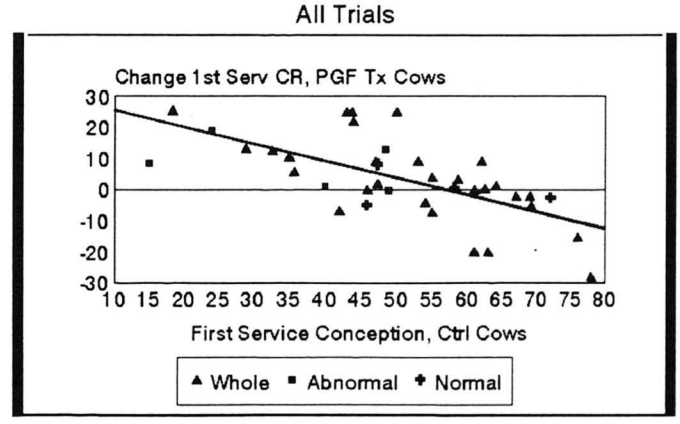

Figure 2. Effect of PGF on Change in First Service conception Rate.

A question that frequently arises is the effect of ovarian status at the time of PGF treatment on the response in reproductive performance of cows to PGF treatment. Four papers have examined this question. Glavill and Dobson, 1991, looked at first service conception rate relative to milk progesterone levels at the time

Table 3. Weighted Averages of Days Open for Untreated and PGF Treated Cows by Category of Trial.

	No. of Studies	PGF Group		Ctrl Group		Ctrl Minus PGF
		Conc Rate	No of Cows	Conc Rate	No of Cows	
Whole Herd Trails	14	51.5	2205	50.8	1800	0.7
Abnormal Peripartum Trials	5	40.5	490	37.6	386	2.9
Normal Peripartum Trials	4	52.9	907	55.2	787	-2.3

of PGF treatment in cows which were selected for peripartum conditions that were likely to adversely affect fertility. The four herds that were selected for the trial had excellent reproductive performance and, as might be expected, progesterone concentration in milk at the time PGF treatment had no effect on first service conception rate in these well managed herds. Etherington, *et al.*, 1988, compared the reproductive performance of cows treated with cloprostenol (CLP) at either 26 days, 40 days, or both 26 and 40 days postpartum with untreated herdmates. Overall, there was a significant reduction in days open for cows treated with CLP at 26 days postpartum and a non-significant reduction when treated at 40 days postpartum. There was a significant improvement in first service conception rate for cows with any CLP treatment. For cows with low milk progesterone at 26 days postpartum, there was a greater advantage to CLP treatment at 26 days than at 40 days but there was still an advantage at 40 days over no treatment. For cows with elevated milk progesterone, there was an advantage to CLP treatment at 40 days postpartum (Table 4). In the trial by McClary, *et al.*, 1989, there doesn't appear to be any effect of serum progesterone status of the cows at the time PGF treatment on subsequent reproductive performance of the cows (Table 5). In the trials of Young and Anderson, 1986, an advantage of PGF treatment was seen in an improvement in the first service conception rate of cows with low blood progesterone and no advantage in the first service conception rate of cows with elevated progesterone (Table 6).

Table 4. The Relationship of Milk Progesterone Concentration at Day 26 on Days Open.

		Treatment			
	Day 26	Placebo	Clp	Placebo	Clp
	Day 40	Placebo	Placebo	Clp	Clp
Days Open, All Cows		149.8 (n=30)	120.6 (n=35)	123.4 (n=31)	114.2 (n=32)
Days Open, P4 > 1 ng/ml		143 (n=14)	137 (n=13)	119 (n=14)	104 (n=23)
Days Open, P4 < 1 ng/ml		155 (n=16)	113 (n=22)	127 (n=17)	140 (n=9)

Adapted from Etherington, et al., 1988.

Interpretation of these studies is limited by the limited numbers of cows in these studies, the differences in experimental designs and differences in reporting results. The most pertinent interpretation is that reproductive performance has been improved whether progesterone status was low or elevated at the time of PGF treatment and of particular interest is that even in cows with low progesterone concentrations at the time of treatment, subsequent conception rate has been improved. This implies that the mechanism of action for PGF treatment in the postpartum cow is not dependent upon luteolysis to improve subsequent reproductive performance. Bonnett, *et al.*, 1990, evaluated the effects of PGF treatment at day 26 postpartum. PGF treatment at day 26 significantly reduced the number of cows with vaginal discharge and reduced the size of the previously gravid uterine horn at day 40. PGF treatment at day 26 significantly decreased the likelihood of isolation of *Actinomyces pyogenes* from endometrial biopsies at day 40.

Table 5. The Relationship of Serum Progesterone Concentration at Day 14 to 16 to Reproductive Parameters (PGF Treatment at Day 14 to 16).

	Low Progesterone	High Progesterone
	P4 < 1 ng/ml	P4 > 1 ng/ml
Days to First Service	70.8 (n=72)	78.1 (n=9)
Days Open	98.4 (n=55)	100.3 (n=6)
Services per Pregnancy	1.67 (n=55)	1.50 (n=6)

McClary, et al., 1989.

Table 6. The Relationship between Blood Progesterone Concentration at Days 14 to 28 to First Service Conception (PGF Treatment 14 to 28 DIM).

	P4 < 0.5 ng/ml	P4 > 0.5 ng/ml
PGF Group	64% 52/81	56% 27/48
Ctrl Group	44% 35/79	55% 26/47

Young and Anderson, 1986.

It is difficult to draw specific conclusions about optimal interval from calving to postpartum PGF therapy. There are few trials in which the interval from calving to PGF treatment was varied within herd and limited numbers of animals for within herd comparison. In the trial by Stevenson and Call, 1988, cows were treated with PGF at either 11-17, 18-25, 25-32, or 33-40 days in milk and subsequent first service conception rate was 30, 28, 19, and 15%, respectively, for cows with ab-

normal peripartum when bred at similar intervals from calving. This suggests that there may be an advantage to earlier treatment postpartum rather than later.

There is limited evidence to suggest there is an advantage to treat cows with an abnormal peripartum twice with PGF at a two week interval. In a study of Archbald, *et al.*, 1990, to evaluate the effect of postpartum PGF treatment at 14 days postpartum on cows having dystocia and/or retained fetal membranes, there was no advantage to postpartum PGF treatment with days open of 137 for the PGF group of 115 cows and 135 days for 114 untreated herdmates. In a later study by Ricco, *et al.*, 1994, selected by a similar criteria, the first service conception rate for 116 cows treated twice with PGF at 12 and 26 days in milk was 43% compared to 24% for 113 abnormal untreated herdmates. Based on limited evidence, the potential of a relatively high benefit and the low cost of two vs one PGF treatment for cows experiencing an abnormal puerperium, it seems rational to recommend two PGF treatments at a two week interval for those cows at high risk of uterine disease.

Conclusions

1. There appears to be no advantage to routinely treating postpartum cows with PGF in herds when days open are less than 100 days.

2. There is a potential reduction in days open through the routine treatment of postpartum cows with PGF when the days open for the untreated herd is greater than 100 days.

3. When there is a reduction in days open as a result of routine treatment of cows with PGF in the postpartum period, the reduction in days open is affected through an improvement in first service conception rate. There is no improvement in first service where conception rate is greater than 50%. The potential advantage of routine treatment of postpartum cows with PGF is in herds where the normal first service conception rate is less than 50%.

4. Numerous factors affect first service conception rate including accuracy of heat detection, fertility of the semen used, technique of the inseminator, and factors affecting cow fertility including nutritional interactions with reproduction. Any one of these factors can become a limitation to first service conception rate and prevent the potential positive impact that routine postpartum PGF therapy may have on first service conception rate.

5. In addition to the potential value that routine postpartum PGF treatment may have on reproductive performance in selected herds, PGF treatment of cows with peripartum health disorders including retained fetal membranes and/or dystocia is likely to benefit the reproductive performance of these cows.

6. One study showed a significant reduction in the isolation of *Actinomyces pyogenes* from the uterus of cows treated with PGF at 26 days postpartum compared to non-treated herdmates when evaluated at 40 days postpartum.

Suggested guidelines for postpartum treatment with PGF

1. Herds should be initially selected based on excessively high days open. Herds which have average days open of greater than 100 days are more likely to benefit from postpartum PGF therapy. The greater days open for the herd, the greater the potential benefit of routine administration of PGF in the postpartum period.

2. The first service conception rate of herds in which average days open are greater than 100 should be evaluated. To get economical response to routine treatment of postpartum cows with PGF, first service conception must improve by roughly 10 percentage points. This means that the herds that are most likely to get an economical response must have first service conception rates of less than 40%.

3. If a program is implemented to routinely treat postpartum cows with PGF, appropriate methods should be implemented to monitor and evaluate the effect of the program on reproductive performance of the herd.

4. Separate from and in addition to the potential role for routine PGF treatment of postpartum cows, there is a role for the use of PGF treatment of cows with peripartum health disorders. These cows should be identified and treated twice with PGF at a two week interval with the first treatment at 14 to 28 days in milk.

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