Prevention of Postpartum Uterine Disease

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Take Home Messages

- Retained placenta, metritis, and endometritis are diseases of immune function in the transition period, starting at least two weeks before calving
- The single largest component of prevention of postpartum uterine disease is to manage transition cows to encourage feed intake
- There are effective antibiotic treatments for cows with metritis, but selection criteria for profitable early or preventive treatment of metritis and endometritis require further research; in the meantime, herd-specific evaluations should be undertaken and protocols developed.

Introduction

Transition period monitoring and treatment programs directed at uterine health should result in more profitable reproductive performance for the herd. With respect to uterine disease, the challenge for producers and advisors is to implement management procedures that result in lower death losses, fewer associated diseases, more milk sold, or a higher herd pregnancy rate. If a preventive or therapeutic action profitably results in at least one of these outcomes, it is justified. Conversely, if reproductive or health management practices cannot be shown to achieve one of these objectives, they should be changed or removed. This paper briefly reviews current information and questions on the causes, impact, treatment, and prevention of retained placenta, metritis, and endometritis in dairy cows.

Retained Placenta

Retained placenta (RP) is failure to pass the placenta (fetal membranes) within 24 hours after calving. The median risk is approximately 9% of calvings. The key element in RP is failure of detachment, which is caused largely if not entirely by impaired immune function before calving. Decreased non-specific immune function occurs 1 to 2 weeks before calving in cows that

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go on to have RP (Kimura et al., 2002). Lack of uterine contractions is not the cause of RP. Abortion, twin birth, induced parturition, dystocia, caesarean section, stillborn calf, and milk fever are all associated with increased risk of RP, but hypocalcemia is not a direct cause. Animals with problematic negative energy balance before calving (evidenced by elevated serum non-esterified fatty acids (NEFA ≥ 0.5 mEq/L)) and/or sub-optimal vitamin E status in the last week before calving are more likely to have RP (LeBlanc et al., 2004).

Retained placenta is a symptom of a suboptimal transition, but is only important to reproductive performance to the extent that it is a substantial risk factor for metritis and endometritis. The impact of RP ranges from none, to impaired reproductive performance, to progression to severe metritis with loss of production. Just as the occurrence of RP depends on immune function, so does the course once the condition has occurred. The best analyses estimate that affected cows become pregnant approximately 15% more slowly than unaffected cows (Fourichon et al., 2000). It is likely that impaired reproductive performance occurs only if metritis or clinical and/or subclinical endometritis result from the RP. Loss of milk production appears to be confined to those individuals that progress to clinical metritis (Fourichon et al., 1999), and RP itself appears not to increase culling risk.

It is important to clearly establish what the objective of treatment is. Although there are conflicting reports, there is no strong evidence that oxytocin, prostaglandin F2α (PGF), or antibiotics hasten the passage of the RP, reduce the risk of displacement of abomasum (DA), or improve subsequent reproductive performance (Frazer, 2005). Historically, manual removal of RP by manipulation and traction was practiced. There is no evidence that this practice produces beneficial results (Drillich et al., 2006b), and some evidence that it is harmful. Several studies indicate that approximately 50 to 80% of cows with untreated RP will have a temperature > 39.5°C on at least 1 day within 10 days postpartum (Stevens and Dinsmore, 1997; Drillich et al., 2003, 2006b). It is not clear if all of these require systemic antibiotic treatment. Several of these studies indicate that daily infusions of 5 g oxytetracycline IU (intrauterine) for as long as the RP is in place reduced the incidence of fever from approximately 50% of cows with RP to approximately 30% of affected cows. In another study, ceftiofur (1.1 mg/kg IM q 24 for 5 d) in cows with RP and fever was as effective (67% absence of fever by 10 days in milk (DIM)) as a combination of systemic and IU ampicillin and manual removal of the placenta; there was no difference in reproductive performance between the two treatments (Drillich et al., 2003).

Typically, 25 to 50% of cows with RP develop metritis. Recent studies consistently indicate that there is no advantage in reproductive performance to automatically treating all cases of RP with systemic antibiotics. There are no trials published in which cows with RP and fever (with or without fetid

discharge) were left untreated, even for 1-2 d. Two published field studies (Risco and Hernandez, 2003; Drillich et al., 2006a) compared treatment with 1 to 2 mg/kg ceftiofur of all cows with RP to treatment of cows with RP only if they progressed to having a fever. There were no differences in culling or subsequent pregnancy rates between the two approaches. Unless most cows with RP will eventually be selected for systemic treatment with antibiotics because they develop metritis, or production is exceptionally high in early lactation, current data indicate that it is economically preferable to selectively treat metritis cases rather than automatically treat all cows with RP with antibiotics. However, this approach depends on a management system and labor that may be relied upon to identify individuals with metritis early in the progression of the disease. Presently, a reasonable protocol may be to treat cows that have at least two symptoms of metritis (fever, dullness or inappetance, or fetid discharge) with 3-5 days of ceftiofur or penicillin systemically. However, the criteria to select cows that will benefit from treatment require further research.

Because the cause of RP is multifactorial, it is important to recognize that no one preventive measure will be universally effective. The principle for prevention is to optimize peripartum immune function, principally through management to encourage feed intake in the transition period. In particular, the prepartum diet should include 0.3 ppm selenium and 1000-2000 IU/cow/d of vitamin E. Among animals with sub-optimum circulating vitamin E in the last week prepartum (serum α-tocopherol:cholesterol ratio $< 2.5 \times 10^{-3}$), injection of 3000 IU a-tocopherol SC or IM one week before expected calving reduced the risk of RP (LeBlanc et al., 2002a). Unfortunately, there is no simple way to identify individuals or herds that may benefit from this treatment. Peripartum oral administration of calcium does not reduce the incidence of RP (Hernandez et al., 1999). Decisions about preventive interventions should consider the magnitude of the problem as well as the evidence for the expected costs and benefits of proposed measures.

■ Metritis

Metritis (puerperal metritis) is inflammation of the uterus resulting in systemic signs of sickness, including fever, red-brown watery foul-smelling uterine discharge, dullness, inappetance, elevated heart rate, and low production (Sheldon et al., 2006). It occurs only in the first two weeks after calving, primarily in the first 7 days. Contamination of the uterus with potentially pathogenic bacteria occurs after calving in almost all cattle, so the development of metritis depends largely on immune function in the early postpartum period (Hammon et al., 2006). Among cows with metritis, E. coli and a variety of anaerobic bacteria are common isolates. The largest risk factor for metritis is retained placenta, but other conditions that may impair feed intake (Urton et al, 2005) and immune function also increase the risk of

metritis.

Affected cattle have moderate to severe illness so there is little dispute that cows with metritis require systemic antibiotic treatment. There are data to indicate that 1 mg/kg ceftiofur maintains therapeutic concentrations (Sheldon et al., 2004b) in uterine tissues in most, though not all treated animals (Okker et al., 2001; Drillich et al., 2006c). More importantly, clinical field trials indicate that the treatments of choice for metritis include ceftiofur (1 to 2 mg/kg IM once per 24 h or procaine penicillin (21,000 IU/kg IM q 12-24 h) for 3 to 5 days (Smith et al., 1998; Drillich et al., 2001; Chenault et al., 2004; Drillich et al., 2006a). Despite pharmacologic evidence against achieving adequate uterine concentrations at label doses (Bretzlaff et al., 1983) a field study reported clinical efficacy of tetracycline at 10 mg/kg (Schmitt et al., 2001). There are not clear data on whether addition of anti-inflammatory drugs improves outcomes over the use of systemic antibiotics alone. One area of controversy is whether there is any benefit to the addition of intrauterine antibiotics to supplement systemic treatment. Clinical field trials indicate that there is no benefit to IU oxytetracycline or ampicillin over systemic ceftiofur or penicillin alone (Smith et al., 1998; Drillich et al., 2003, 2006b).

Treatment of metritis appears to be justified on the grounds of cow welfare and reduction of the probability of death in severe cases. However, the criteria for success are inconsistent. Ideally, the objective is to quickly return cows to their expected level of production with no other complications. From recent studies, the expected outcome is removal of fever in 67 to 77% of treated animals by 5 to 10 days after treatment. There is a lack of data on the efficacy of treatment of metritis for prevention of subsequent related diseases (e.g. displaced abomasum) or for improvement of eventual reproductive performance. Furthermore, it is not clear whether systematic programs aimed at early diagnosis and treatment of metritis are effective in preventing progression to severe disease with losses in performance, or whether they result in treatment that is not medically or economically beneficial. For example, ceftiofur HCl (2.2 mg/kg IM q 24 for 5 d) administered starting at 1 day post calving to cows with RP without regard to body temperature significantly reduced the incidence of fever with fetid discharge, with no effect on time to pregnancy (Risco and Hernandez, 2003). In attempting early diagnosis of metritis, attention must be paid to normal uterine involution. For example, abundant red-brown lochia is normal in the first two weeks postpartum. Additionally, fever of 1 to 2 days duration is common in the first week after calving and is not well correlated with uterine infection (Sheldon et al., 2004a). Observation of cows' attitude, appetite (if possible), and daily milk production are likely useful screening tests to select cows for further examination. Cows with RP should be inspected daily until the placenta is passed to detect progression to metritis. Measurement of rectal temperature is indicated in cows that are dull, inappetant, producing less milk than

expected, or declining in milk production. More large-scale field studies are needed to validate criteria for preventive or early treatment of metritis.

■ Endometritis

Bacterial contamination of the uterus is almost universal in the first two weeks postpartum (Sheldon, 2004). While there are good reasons to have cows calve in a clean environment, it is very unlikely that bacterial infection of the uterus can be prevented altogether. However, healthy cows clear bacteria from the uterus within approximately 3 weeks after calving, and complete involution of the uterus and cervix within 4 to 6 weeks. Therefore, the objective of management is to optimize immune function to allow cows to clear the inevitable bacterial load from the uterus.

For reproductive examinations before the breeding period to have value, they must identify cows at increased risk of failure to become pregnant in a timely way and that may benefit from treatment. Endometritis is a localized inflammation of the endometrial surface of the uterus without systemic signs, associated with infection of the uterus with pathogenic bacteria, primarily *Arcanobacterium pyogenes*, which persists for more than 3 weeks postpartum. Clinically, the challenge is to identify those cows that are truly at risk of impaired fertility, and to administer treatment that mitigates the problem.

To derive a clinical definition of endometritis, data were collected from 1865 cows in 27 herds, including history of dystocia, twins, RP, or metritis (LeBlanc et al., 2002b). All cows were examined once between 20 and 33 DIM including external inspection, vaginoscopy, and palpation of the cervix, uterus and ovaries. Survival analysis was used to derive a case definition of endometritis based on factors associated with increased time to pregnancy, and to measure the effect of treatment. Clinical endometritis was diagnosed by the presence of purulent uterine discharge or cervical diameter greater than 7.5 cm after 20 DIM, or mucopurulent discharge after 26 DIM. Given vaginoscopy, no diagnostic criteria based on palpation of the uterus had predictive value for time to pregnancy. The prevalence of clinical endometritis was 17%. Vaginoscopy was required to identify 44% of these cases, but other methods of examining discharge from the cervix are likely also effective (Sheldon et al., 2002; McDougall et al., 2006). Accounting for parity, herd, and ovarian status, cows with clinical endometritis took 27% longer to become pregnant, and were 1.7 times more likely to be culled for reproductive failure than cows without endometritis (LeBlanc et al., 2002b).

The principle of therapy of endometritis is to reverse inflammatory changes that impair fertility by reducing the load of pathogenic bacteria and enhancing the processes of uterine defence and repair. There are few well-designed,

appropriately analyzed, large-scale field studies of the diagnosis and treatment of endometritis with both an objective case definition and economically meaningful outcomes. Many trials suffer from a lack of negative controls, small numbers of animals resulting in little statistical power, or diagnostic criteria that were not validated as to their effect on reproductive performance, making it difficult to discern a true treatment effect.

One approach to treatment of endometritis is to administer one or more injections of PGF. Progesterone is generally favourable for the maintenance of uterine infection; whereas many aspects of going through estrus are plausibly favourable for prevention or clearance of uterine infection. There are numerous studies that report improved reproductive performance when cows were routinely given at least 1 injection of PGF between 14 and 40 DIM (e.g., Bonnett et al., 1990). There are also numerous studies that report no benefit of routine postpartum PGF (e.g., Stevenson and Call, 1988). A meta-analysis of studies on postpartum PGF revealed a statistically significant but small (2 to 3 days) reduction in days open in treated dairy cows (Burton and Lean, 1995). There is little evidence to support the use of PGF before 3 weeks postpartum (Kristula and Bartholomew, 1998; Hendricks et al., 2006), but, on balance, reasonable support for routine use of PGF at approximately 4 and 6 weeks postpartum in herds with a high prevalence of RP and metritis (Bonnett et al., 1990). There is a lack of evidence for improved reproductive performance among cows with endometritis treated with PGF (e.g., Benmrad and Stevenson, 1986; Risco et al., 1994; LeBlanc et al., 2002c). However, many of these studies lacked statistical power to discern treatment effects. Conversely, PGF was at least as effective as some intrauterine antibiotic treatments (Steffan et al., 1984; Sheldon and Noakes, 1998), although these studies lacked untreated controls.

The other approach to treatment of endometritis is intrauterine administration of antibiotics. There is not evidence of improved reproductive performance among cows with endometritis treated with IU penicillin or tetracycline, relative to treatment with PGF or to no treatment (Steffan et al., 1984; Thurmond et al., 1993; Sheldon and Noakes, 1998). However treatment of cows with specifically diagnosed clinical endometritis after 4 weeks postpartum with 500 mg cephapirin IU resulted in a significantly shorter time to pregnancy than in untreated cows (63 % relative increase in pregnancy rate; LeBlanc et al., 2002c). Similarly, among seasonally-bred dairy cows with specific postpartum risk factors, treatment with cephapirin at approximately 6 weeks postpartum increased the proportion pregnant by 56 days into the breeding season (McDougall, 2001).

Subclinical endometritis, diagnosed by cytology, appears to affect 35 to 50% of cows between 35 and 60 DIM and is associated with substantially reduced pregnancy rate (Kasimanickam et al., 2004; Gilbert et al., 2005). Treatment with either cephapirin IU or PGF improved pregnancy rate in cows with

subclinical endometritis (Kasimanickam et al., 2005). Ultrasound examination may be used to identify some, but not all cases. While cytology to diagnose subclinical endometritis is not practical for routine use in the field, the high prevalence and impact of this condition merit consideration. Cow-side diagnostics or surrogate measures of subclinical endometritis would facilitate quantification of the prevalence of the problem and evaluation of treatment.

There are valid criteria to diagnose endometritis, and treatments proven to improve pregnancy rate. Treatment of postpartum endometritis should be reserved for cases diagnosed after 4 weeks postpartum based on criteria that are associated with subsequent pregnancy rate. Further research is needed on the optimal timing and the need for repeated administration of PGF2α as a treatment for endometritis. The value of the effort for individual diagnosis and treatment is herd-specific and depends on the sensitivity and specificity of the diagnostic criteria, the prevalence of endometritis, and the cost and efficacy of treatment. However, despite their shortcomings, taken together, several recent studies (Tenhagen and Heuwieser, 1999; Heuwieser et al., 2000; Kasimanickam et al., 2006) indicate that a program of 2 injections of PGF at approximately 35 and 49 days postpartum without individual examination, followed by either intensive heat detection or timed insemination, is the standard against which other uterine health management programs should be compared economically.

■ Conclusions

Retained placenta, metritis, and endometritis are diseases of immune function in the transition period, which begin at least 2 weeks prepartum. Accordingly, they are multifactorial and no one preventive measure will be universally effective. The principle for prevention is to optimize peripartum immune function, principally through management to encourage feed intake in the transition period (e.g., >3 week close-up period with minimal group changes, >30” bunk space, <85 % stocking density; heat abatement when the temperature-humidity index is > 72; Cook and Nordlund, 2004; Urton et al., 2005). The transition diet should include 0.3 ppm selenium and 1000-2000 IU/cow/d of vitamin E. Fortunately, the management procedures aimed at prevention of postpartum uterine disease are essentially the same as those to favor other aspects of health and production in transition cows.

While more research is needed to develop selection criteria for profitable treatment of early cases of metritis, a reasonable protocol based on available information may be to treat cows with at least two symptoms (RP, fever (T > 39.5 °C), dullness or inappetance, and fetid uterine discharge) with 3 to 5 days of systemic ceftiofur or penicillin. Automatic antibiotic treatment of all cows with RP is not beneficial in many circumstances. While clinical and subclinical endometritis cause substantial impairment of reproductive

performance in affected cows, the economic benefit of efforts to identify and treat these individuals is herd-specific.

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