Interaction between Clinical Mastitis, Other Diseases and Reproductive Performance in Dairy Cows

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Take Home Messages

- Metabolic disorders and mastitis cause economic losses to dairy producers, with negative effects going beyond losses in milk production to impact the reproductive performance of dairy cattle.
- Although one particular metabolic disorder by itself may not have a large effect on reproduction, multiple disorders can exacerbate the cow's health and have additive detrimental effects on reproduction. Therefore, it is of utmost importance that all metabolic disorders be prevented.
- The detrimental effects of clinical mastitis on reproduction are more evident when cows experience both clinical mastitis and other diseases.
- Producers should pay extra attention to mastitis prevention and control, especially around the time of breeding. This is not only for the benefit of milk production efficiency, but also reproductive efficiency.

Introduction

Reproductive efficiency is an important contributor to dairy farm profitability. Unfortunately, the reproductive performance of dairy cattle has declined steadily over the last few decades (Lucy, 2001). Many factors influence dairy cow fertility including climate and environment, herd characteristics and herd management, genetics and incidence of various diseases. The effect of diseases on reproduction has received more attention during the last 10 years. It has become more evident that reproductive disorders such as dystocia, retained placenta, ovarian cysts and metritis can decrease reproductive performance of dairy cows. It may not be surprising that diseases that affect reproductive systems can directly affect reproductive performance. However, the effects of other diseases, such as metabolic

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disorders and mastitis, on dairy cow fertility have not been quantified. Moreover, the majority of the studies that have investigated the relationship between metabolic disorders, mastitis, and reproduction have only established associations and were unable to infer causality because it is difficult to control other confounding effects. This paper highlights the effect of some of the metabolic disorders on reproduction. Moreover, we discuss in more detail the effect of mastitis on reproduction and the possible mechanism by which mastitis pathogens affects reproduction. Lastly, we have briefly highlighted preventative and management practices that help to reduce the incidence of metabolic disorders and mastitis so that both production and reproductive performance of the dairy herd can be improved.

■ Metabolic Disorders and Reproductive Performance

Milk Fever

Milk fever and subclinical hypocalcaemia perhaps are important predisposing factors that lead to increased incidence of several other transition cow disorders. For example, cows with milk fever were up to eight times more likely to develop mastitis in the following lactation, three times more likely to develop dystocia and retained placenta, and two to four times more likely to develop abomasal displacement (Mulligan et al., 2006). On average, 5-10% of dairy cows have clinical milk fever, suggesting that the incidence of subclinical hypocalcaemia may reach 33% (reviewed in Mulligan et al., 2006). The majority of research appears to indicate that the effect of milk fever on reproduction is moderate. According to a meta-analysis (Fourichon et al., 2000), cows with milk fever had increased days to first service (approximately 5 days) and increased services per conception (0.3 services); however, overall days open and conception rate had no association with milk fever. In contrast, a recent study showed that cows not having milk fever were 2.25 times more likely to conceive than those that had milk fever (Chebel et al., 2004). Theories as to how milk fever results in reduced fertility in dairy cows include alteration in uterine muscle function, slower uterine involution, and reduced blood flow to the ovaries (Figure 1). There are also indirect effects of milk fever on fertility, which are mediated through dystocia, retained placenta and endometritis (reviewed in Mulligan et al., 2006).

Overall, it appears that cows with milk fever may be at increased risk of infertility compared with their healthy herdmates. The most important preventative measure for reducing the risk of milk fever is to feed a proper ration, especially during the close-up period (3 to 4 weeks before calving). The diet should be balanced for proper dietary cation-anion difference (DCAD) and contain dietary potassium at recommended levels. If producers cannot provide diets with potassium at recommended concentrations, then

feeding anionic salts should be considered.

Ketosis and Displaced Abomasums

Subclinical and clinical ketosis are problems in modern dairy herds. A prevalence of 12 to 14% has been reported in North American dairy cows and a wider range of 7 to 32% worldwide (reviewed by Cook et al., 2001). Ketosis caused by marked glucose insufficiency and increased fat mobilization, which may adversely affect cow fertility. This negative effect may be expected considering the implications of metabolic and biochemical changes that can occur during ketosis. However, the effect of ketosis on reproductive performance varied among studies. Using ten peer-reviewed studies, the association between clinical ketosis and reproductive performance was investigated by meta-analysis (Fourichon et al., 2000). The meta-analysis revealed that clinical ketosis appeared to increase days to first insemination by 2.5 days and days open by approximately 6 days and decrease conception to first service by 3.8 percentage points. Moreover, the hazard ratio of conception between 56 and 120 days postpartum was 13% less for cows with clinical ketosis. In the same study, however, the authors found that in Holstein cows from the US or Canada, ketosis had no significant effect on reproduction, but a small association was detected in Swedish Red and White and Swedish Friesian cows. The authors (Fourichon et al., 2000) suggested that the effects of clinical ketosis on reproduction are limited, but show large variation in different production systems.

Cook et al. (2001), however, detected very significant reductions in reproduction due to clinical ketosis. Cows with ketosis had significantly longer days open (139 vs. 85 days) and greater culling rate due to a failure to conceive. In a more recent study (Walsh et al., 2007), cows with elevated beta-hydroxybutyrate (BHBA) concentrations, indicating severe subclinical ketosis, during the first and second weeks postpartum were 50% less likely to be pregnant after the first insemination. Moreover, median days open was 16 to 20 days longer for cows with subclinical ketosis compared with healthy cows. These authors (Walsh et al., 2007) concluded that the circulating concentration of BHBA and the duration of elevated circulating BHBA were inversely associated with the probability of pregnancy at first service.

Prevention of ketosis is also related to nutritional management of the cows during the transition period (-3 to +3 weeks postpartum). A critical point in ketosis prevention is to provide adequate dietary energy, minimize the reduction of dry matter intake during the last 3 weeks prepartum, and maximize dry matter intake after calving. After careful consideration and economic evaluation, feeding additives such as niacin, calcium propionate, propylene glycol, and rumen-protected fat or choline may be beneficial in preventing ketosis. Preventing dystocia and other metabolic disorders also reduces the risk for ketosis.

Prevention Strategies are Essential

Collectively, it appears that metabolic disorders modestly affect fertility of the dairy cow. Unfortunately, the occurrence of the above mentioned disorders can increase the risk of other metabolic disorders as well as several reproductive maladies such as dystocia, retained placenta, and metritis (Figure 1). Hence, where one particular metabolic disorder by itself may not have a large effect on reproduction, it can exacerbate the cow's health and consequently have additive detrimental effects on reproduction. For example, it has been reported that cows that had milk fever are up to eight times more likely to develop mastitis in the following lactation, three times more likely to develop dystocia, and two to four times more likely to develop displaced abomasum. Therefore, it is essential that all metabolic disorders be prevented. Producers, veterinarians, nutritionists and farm consultants should not only focus on disease outcomes, such as milk yield and fertility, but also review 'up-stream' factors such as management practices, nutritional regimens and health status, especially during the transition period. It is still quite common to find farms that have no standard operating procedures or strategies to prevent and control fresh cow problems. Monetary losses (seen as decreased milk production and decreased reproductive efficiency) due to ketosis, milk fever and displaced abomasum justify having an intense fresh cow management program. In addition to the previously mentioned strategies to minimize metabolic disorders such as milk fever and ketosis, overcrowding cows, especially in the fresh cow pen, must be avoided to allow for the maximization of dry matter intake for each cow.

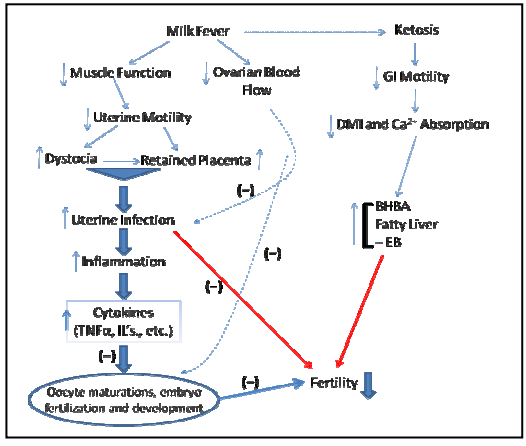

Figure 1. Potential mechanisms by which milk fever and ketosis affect fertility.

■ Mastitis and Reproductive Performance

Mastitis is defined as inflammation of the mammary gland, and can be triggered by many factors such as trauma and (or) injury to the udder, infection due to microorganisms, and chemical irritation (Philpot and Nickerson, 2000). Management strategies that have been followed since the 1960's have made substantial improvements in controlling contagious pathogens and have been somewhat effective against environmental pathogens. Nonetheless, intra-mammary infections caused by microorganisms are still a major problem, even in well-managed dairy farms. Mastitis is still the most costly disease in dairy farms (Table 1) because of reduced milk production, increased involuntary culling rate, and discarded milk (Philpot and Nickerson, 2000). Indeed, it has been estimated (DeGraves and Fetrow, 1993) that costs associated with mastitis for the US dairy industry are over 2 billion US dollars per year.

The direct costs of clinical mastitis due to the above mentioned reasons (Table 1) are rather obvious. What producers may not notice is the indirect cost stemming from reduced reproductive performance. Studies confirm that mastitis has detrimental effects on reproductive efficiency of dairy cows and thus negatively affects the profitability of dairy herds.

Table 1. Estimated annual loss due to mastitis.

Source of loss	$US loss per cow	Percent of total
Reduced milk production	$121.00	66.0
Discarded milk	$10.45	5.7
Early replacement cost	$41.73	22.6
Extra labor	$1.14	0.1
Drugs	$7.36	4.1
Veterinary services	$2.72	1.5
Total	$184.40	100

Adapted from Philpot and Nickerson, Winning the Fight Against Mastitis. 2000. Westfalia Surge, Inc., Naperville. IL

Clinical Mastitis and Reproductive Performance

Reproductive efficiency is of great concern to dairy producers because the loss of potential income for each day a cow remains non-pregnant, over 100 days in milk (DIM), has been estimated at $US 0.42 to $US 5.00 per day, depending on stage of lactation (Fetrow and Blanchard, 1987; French and Nebel, 2003).

Preliminary field evidence (Moore et al., 1991) suggested that clinical mastitis

may indirectly impair reproductive performance in dairy cows due to alteration of inter-estrus intervals and shortening of the luteal phase (premature luteolysis) (Table 2). Barker et al. (1998a) showed that the onset of clinical mastitis before first AI increased days to first service and days open (DO), but did not affect services per conception (S/C). The same researchers (Barker et al., 1998b) reported that when clinical mastitis occurred between first AI and conception, both DO and S/C increased significantly compared to uninfected cows. Schrick et al. (2001) showed that cows with mastitis before first service had an extended number of days to first AI, increased DO and S/C compared to uninfected cows. Schrick et al. (2001) also reported that cows with mastitis between first AI and pregnancy confirmation had increased DO and S/C in comparison to the healthy group (Table 2). Risco et al. (1999) reported that cows with clinical mastitis within the first 45 days of gestation were at 2.7 times greater risk of abortion within the next 90 days than uninfected cows. Similarly, Chebel et al. (2004), following evaluation of health records of 1400 Holstein cows, showed that the occurrence of clinical mastitis within the time frame of the day of AI to pregnancy reconfirmation was associated with increased pregnancy loss, such that cows having clinical mastitis were 2.8 times more likely to lose their pregnancy than those not experiencing mastitis.

In a retrospective study, Santos et al. (2003,a,b) found that cows that experienced clinical mastitis prior to first postpartum AI and cows that experienced clinical mastitis between first postpartum AI and pregnancy confirmation had extended DO. Moreover, culling rate was increased in cows with mastitis compared with uninfected cows. Furthermore, cows with mastitis, anytime in lactation, had a greater incidence of abortions. Therefore, it appears that mastitis, either prior to or after first postpartum AI, increases culling rate and decreases reproductive efficiency in dairy cows.

Table 2. The effect of mastitis on reproductive performance in dairy cows.

Source	Reproductive Parameters	Mastitis	Uninfected
Moore et al. (1991)	Altered inter-estrus intervals		
	Farm 1	No difference between infected and uninfected	
	Farm 2	Infected cows were 1.6 times more likely to have irregular estrous cycles as compared to uninfected cows	
Barker et al. (1998[a])	Days open	114 ± 10	92 ± 4.6
	Services per conception	1.6 ± 0.3	1.7 ± 0.1
Barker et al. (1998[b])	Days open	136 ± 11	92 ± 4.6
	Services per conception	2.9 ± 0.3	1.7 ± 0.1
Risco et al (1999)	Abortion	Infected cows within the first 45 days of gestation were at 2.7 times more risk of abortion as compared with uninfected cows	
Shrick et al (2001)	Days open	110 ± 6.9	85.4 ± 5.8
	Services per conception	2.1 ± 0.2	1.6 ± 0.2
	Conception rates	48%	63%
Kelton et al (2001)	Conception rates	38%	46%
Santos et al (2003[a])	Days open	165 ± 5.7	140 ± 3.7
	Services per conception	2.6 ± 0.1	2.6 ± 0.1
	Conception rate at 1st AI	22%	29%
Santos et al. (2003[b])	Days open	189 ± 7.2	140 ± 3.7
	Services per conception	3.0 ± 0.2	2.6 ± 0.1
	Conception rate at 1st AI	10%	29%

[a]Based on clinical mastitis before 1st service
[b]Based on clinical mastitis between the 1st AI and pregnancy diagnosis (30 – 40 days post AI)

Research in Idaho

While above studies (Table 2) have indicated that clinical mastitis has harmful effects on reproductive efficiency of dairy cows, none of these studies

provides information on whether cows with mastitis also experienced other diseases. A meta-analysis of previously published research (Fourichon et al., 2000) revealed that other diseases negatively affected reproduction while mastitis had no effect on reproductive performance. Hence, it cannot be ascertained whether the observed decrease in reproductive efficiency in the previous studies (Table 2) was solely due to mastitis. The objective of our research was to evaluate the effect of clinical mastitis and (or) other diseases on reproductive performance in lactating Holstein cows. Records from 967 lactating Holstein cows from a commercial dairy farm in Southern Idaho were used in this study. Diseases other than mastitis included ovarian cysts, retained placenta, left displaced abomasum, ketosis, milk fever, metritis and pyometra, all of which were diagnosed by the herd veterinarian. Retrospectively, cows were divided into four groups according to the presence or absence of clinical mastitis and other diseases: cows with clinical mastitis and other diseases (MD); cows with clinical mastitis only (M); cows with other diseases only (D); and cows with no record of clinical mastitis and other diseases (healthy cow; H). Reproductive parameters of interest included: days open (DO), days in milk at first breeding (DIMFB), and services per conception (S/C). A non-linear regression technique was used to determine the effects of clinical mastitis and (or) other diseases on the proportion of cows that remained non-pregnant from 56 to greater than 224 days in milk.

Results are depicted in Table 3 (Ahmadzadeh et al, 2009). Average DO and S/C were significantly greater for cows that experienced both mastitis and other diseases (MD) and for cows with mastitis alone (M) compared with healthy cows (H). Cows with diseases other than mastitis (D) were not different from healthy cows (H) while S/C and DO of cows with MD and M were similar. These findings suggest that clinical mastitis alone affected reproductive performance by increasing DO and S/C. There was no effect of group on DIMFS, which ranged from 65 to 73 days for all four groups. In contrast, Schrick et al. (2001) and Santos et al. (2004) reported that DIMFB were significantly increased when mastitis occurred before the end of the voluntary waiting period. The observed difference between our study and the results of Shrick et al. (2001) and Santos et al. (2004) could be due in part to breed differences and the breeding programs used in these studies.

Table 3. Least Square means (± SEM) of services per conception (S/C), days open (DO), and days in milk at first breeding (DIMFB) in Holstein cows with or without mastitis or other diseases.

Items	Group[1]			
	MD (n=54)	M (n=154)	D (n=187)	H (n = 572)
DIMFB	73 ± 4.9	66 ± 1.4	65 ± 1.2	67 ± 0.6
S/C	2.8^{a} ± 0.40	2.1^{ab} ± 0.10	1.9^{abc} ± 0.12	1.6^{c} ± 0.06
DO	155^{a} ± 15.0	140^{a} ± 5.30	97^{b} ± 4.55	88^{b} ± 2.16

[1]MD = Cows that had both clinical mastitis and other diseases; M = Cows that had clinical mastitis only; D = Cows that had diseases other than mastitis; H = Healthy cows that did not have either clinical mastitis or other diseases.
[a,b,c]Within a row, means with different superscripts differ (P<0.05).

The predicted exponential lines for the proportion of cows that remained non-pregnant during 224 days postpartum and the final estimated proportion of non-pregnant cows at 224 days in milk (DIM) are in Figure 2. The estimated rate of decline (5 non-pregnant cows over time) for groups MD and M was significantly lower than that of H, indicating a smaller proportion of cows became pregnant over time in the MD and M groups compared with cows in the H group. For instance, by 160 days postpartum, a higher proportion of cows in groups MD and M were still open as compared with uninfected cows (55.3 and 48.5 vs. 33.5%, respectively). The proportion of cows that became pregnant over time for D appeared to be marginally (P = 0.10) less than those for H and closer to M. Moreover, the rate by which cows became pregnant for MD tended (P = 0.10) to be less than those for M. Finally, the estimated proportion of cows that remained open by 224 DIM was greater in MD, M and D compared with H. This implies that a greater proportion of cows are at risk of being removed from the herd if they experience clinical mastitis and (or) other diseases because they may not become pregnant in a timely manner.

Our results suggest that reproductive efficiency was decreased by the presence of clinical mastitis in that a greater proportion of cows with mastitis remained non-pregnant over time. Furthermore, the negative effects on reproduction were exacerbated when cows experienced both clinical mastitis and other diseases.

Economically the effect of mastitis on reproduction is alarming. Regardless of experimental design, breeds, and locations, the studies included in Table 2 appear to indicate that the number of days open in cows with mastitis were 22 to 49 days longer than uninfected cows. Assuming the additional cost per day open over 100 DIM is approximately $US 2.00 per day, the estimated additional monetary loss for a cow with mastitis is between $US 44 to 98.

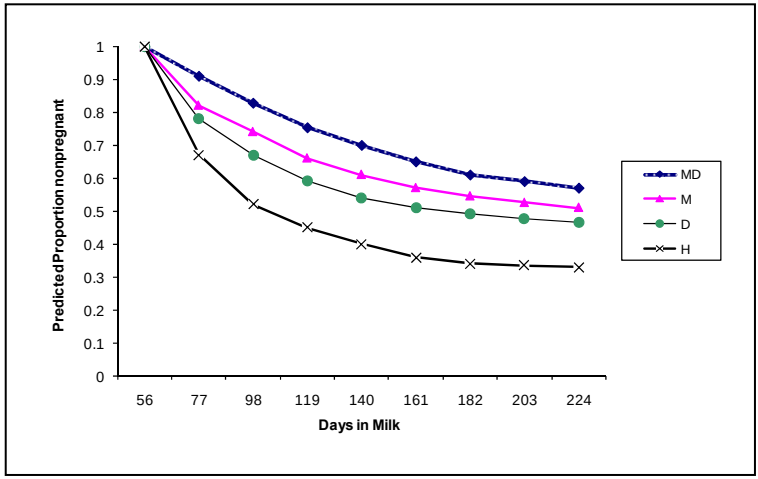

Figure 2. Predicted exponential models ($Y_{ij} = (1\text{-}C) \times e^{-\beta i\,(Xj-56)} + C_i$) for the proportion of cows that remained open from 56 to 224 days postpartum. Cows were separated into four groups: MD (-♦-) = Cows that experienced both clinical mastitis and other diseases; M (-▲-) = Cows that experienced clinical mastitis only; D (-●-) = Cows that experienced diseases other than mastitis; H (-×-) = Cows that did not experience either clinical mastitis, or other diseases.

How does Mastitis Affect Reproduction?

How mastitis affects reproductive performance is not completely understood, although possible mechanism(s) have been theorized (Figure 3). Cells harvested from milk of infected mammary glands have elevated levels of cytokines including tumor necrosis factor-α (TNF-α), and nitric oxide (NO) and a variety of interleukins (reviewed in Hansen et al., 2004). Intra-mammary infusion of E. coli endotoxin (LPS) and Streptococcus uberis resulted in increased concentrations of $PGF_{2\alpha,}$ TNF-α, and NO in blood or milk. These investigators suggested that increased $PGF_{2\alpha}$ in infected cows may cause premature luteal regression and (or) may have detrimental effects on embryonic development and quality, causing increased embryonic loss, and consequently, increased S/C and DO. Interestingly, it has been suggested that LPS, TNF-α , NO, and $PGF_{2\alpha}$ can affect a cow's fertility by negatively affecting bovine oocytes and (or) the bovine developing embryo (reviewed in Hansen et al., 2004).

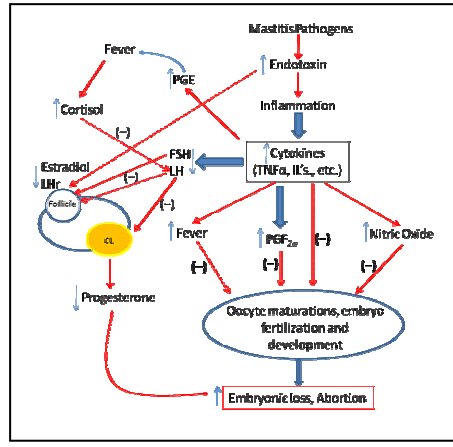

Figure 3. Potential mechanisms by which mastitis affects fertility.

Shuster and Kehrli (1995) reported that infusion of E. coli into the mammary gland of dairy cows resulted in elevated levels of cytokines (interleukin-1) in milk. It has been suggested (McCann et al., 1997) that cytokines may block follicle stimulating hormone (FSH) action and the pulsatile secretion of luteinizing hormone (LH). Both LH and FSH are important for follicular growth and maturation, ovulation, and progesterone and estrogen synthesis. Moreover, LH and FSH are involved in oocyte maturation, cumulus cell expansion, and nourishment of the oocyte (Zuelke and Brackett, 1994). Therefore, mastitis could influence reproductive function by altering LH and FSH activity and (or) function, thus affecting preovulatory follicular development, oocyte maturation and (or) steroidogenesis. Recent research in Israel (Lavon et al., 2009) showed that acute clinical mastitis induced by Gram-negative endotoxin (LPS) caused immediate attenuation of preovulatory follicle steroid concentrations and low mRNA expression of LH receptors; however, LPS did not induce a carryover effect. In contrast, acute clinical mastitis induced by Gram-positive toxin caused both immediate and carryover attenuation of preovulatory follicle steroid concentrations and low mRNA expression of LH receptors.

The detrimental effect produced by clinical mastitis may be related to embryo development and (or) embryonic death. Thatcher et al. (1997) and Lucy (2001) suggested that premature luteal regression during the first month of gestation would likely result in decreased conception rates or increased pregnancy losses in lactating dairy cows. Chebel et al. (2004), in a study investigating embryonic mortality between 31 and 45 days after AI, reported an increase in the incidence of pregnancy loss when clinical mastitis occurred between AI and pregnancy confirmation. The fact that bacterial products such as LPS, and elevated cytokines can affect embryonic development in vitro

support the theory that mastitis can increase the incidence of embryonic loss.

The aforementioned studies have attempted to describe how mastitis can produce homeostatic alterations of endocrine profiles (LH, FSH, $PGF_{2\alpha}$, progesterone, cortisol) as well as alteration of the immune response, thereby affecting oocyte maturation, follicular development, and luteal life span, and ultimately embryonic quality and development. Clearly, the above factors may interact and collectively impact reproductive efficiency.

Summary

Decreased reproductive efficiency has a detrimental effect on the profitability of dairies. Although it is well known that mastitis causes economic losses due to reduced milk production, increased involuntary culling rate, and discarded milk, it is also apparent that the effects of mastitis go beyond losses in milk production and can ultimately reduce reproductive efficiency. Hence, producers should pay extra attention to mastitis prevention and control, not only from the point of view of milk production efficiency, but also reproductive efficiency. Based on our findings it appears that clinical mastitis alone affects reproductive performance. Furthermore, the negative effects of clinical mastitis on reproduction are more evident when cows experience both mastitis and other diseases. Moreover, while producers should manage their herds to prevent and control mastitis, extra attention should be paid when clinical mastitis occurs during the AI period and pregnancy establishment.

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