

MASTITIS EFFECTS ON REPRODUCTION

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Introduction

Mastitis is the inflammation of the mammary gland, which is usually correlated with intramammary infection (IMI) by bacteria or fungi, being the first more common. Clinical mastitis is manifested by secretion of abnormal milk (i.e. watery milk, presence of flakes in milk, etc.) and/or inflammation (i.e. redness, swelling, hardness, etc.) of the mammary gland. Because it is accepted that the normal mammary gland has somatic cell count (SCC) of less than 200,000 cells/mL (linear somatic cell count, LSCC, less than 4) and no bacterial infection, in many circumstances, cows that have SCC greater than 200,000 cells/mL (LSCC > 4) and/or bacteria in the milk, but do not have clinical signs of mastitis, are considered to have subclinical mastitis. The costs associated with mastitis are innumerable and include antibiotic treatment, milk discarded, reduced milk quality (i.e. increased somatic cell count), increased culling rates, and reduced milk yield. Another cost that incurs from occurrence of mastitis that is often taken for granted, however, is reduced fertility. Although a direct causal effect of mastitis on reproductive inefficiency has not been established, it is evident that a correlation between mammary gland health and fertility of lactating dairy cows exists.

Effects of Mastitis on Reproductive Parameters

Most of the studies in which the effects of mastitis on reproductive performance were evaluated are retrospective studies and diagnosis of clinical mastitis and recording of mastitis events were performed by farm personnel. Therefore, it is important to note that inherent variations in diagnosis and recording of mastitis events among studies exist and may account for differences in reported findings. Regardless of possible variations in diagnosis and recording among studies, however, the majority of researches demonstrate a negative correlation between mastitis and fertility.

One of the first studies to demonstrate a correlation between occurrence of mastitis and altered reproductive pattern of dairy cows was performed by Moore et al. (1991). In this study, Holstein cows from two dairy herds were classified as experiencing or not experiencing mastitis between artificial inseminations (AI) or estrus. Cows in herd 1 were affected by *Staphylococcus aureus* (gram-positive bacteria) while cows in herd 2 were affected by coliform mastitis (gram-negative bacteria). The outcome evaluated was inter-estrus interval and cows were classified as having an abnormal inter-estrus interval when it was smaller than 18 d or greater than 24 d. This parameter has commonly been used as an indicator of early embryonic wastage or altered luteal function. Although there was no effect of mastitis on inter-estrus interval in herd 1, cows in herd 2 that experienced mastitis were more likely to have an altered inter-estrus interval compared with cows that did not experience mastitis (Moore et al., 1991). From these findings authors suggested that the gram-negative IMI observed in herd 2 could have affected the inter-estrus interval through endotoxemia (absorption of bacteria produced toxins by the mammary gland), fever, and

systemic secretion of hormones (i.e. prostaglandin F_{2α} and cortisol) that affect luteal and ovarian function (Moore et al., 1991).

A study conducted at the University of Tennessee Dairy Experiment Station research herd further explored the correlation between occurrence of mastitis and reproductive efficiency of dairy cows. Barker et al. (1998) classified lactating Jersey cows as experiencing no mastitis or as experiencing mastitis before first postpartum artificial insemination (FPAI), between FPAI and pregnancy diagnosis, and after pregnancy confirmation. Cows were followed until 150 days in milk (DIM) and pregnancy was confirmed by palpation per rectum 50 to 65 d after AI. The interval between calving and FPAI was greater for cows that had mastitis prior to FPAI compared with the other cows combined (93.6 ± 5.6 and 71.0 ± 2.2 d, respectively). Cows that experienced mastitis between FPAI and pregnancy diagnosis had increased services per conception (SPC, 2.9 ± 0.3 d) compared with cows that had mastitis prior to FPAI (1.6 ± 0.3) and cows that had mastitis after pregnancy confirmation or those that did not have mastitis (1.7 ± 0.1 d). Furthermore, cows that had mastitis prior to FPAI (113.7 ± 10.8 d) and between FPAI and pregnancy diagnosis (136.6 ± 13.3 d) had greater interval from calving to conception (DOPN) compared with cows that experienced mastitis after pregnancy confirmation or those that did not have mastitis (92.1 ± 4.6 d). Interestingly, the correlation of mastitis and fertility was independent of type of bacteria causing the mastitis (gram-positive or gram-negative).

The same group from the University of Tennessee conducted a subsequent study in which they evaluated the correlation between subclinical and clinical mastitis and fertility. In this study, Jersey cows were grouped as not experiencing mastitis, as experiencing subclinical mastitis (bacteria isolated from milk samples but no alterations in milk or mammary gland), or as experiencing clinical mastitis (Schrick et al., 2001). Cows were further divided according to mastitis type (gram-positive or gram-negative) and to the timing of the mastitis event (before FPAI, between FPAI and pregnancy diagnosis, or after pregnancy confirmation). Cows that did not experience mastitis were grouped together with the cows that experienced it after pregnancy confirmation. Similarly to the findings of Barker et al. (1998), cows that experienced clinical or subclinical mastitis before FPAI had extended interval between calving and FPAI (75.7 ± 1.8 d) compared with cows that were uninfected or cows that had mastitis after pregnancy confirmation (67.8 ± 2.2 d). Cows that had mastitis between FPAI and pregnancy diagnosis had intermediate calving to FPAI interval (75.2 ± 4.4 d). Furthermore, the SPC and DOPN were greater for cows that experienced mastitis between FPAI and pregnancy diagnosis (3.1 ± 0.3 and 143.5 ± 11.4 d, respectively) followed by those cows that experienced mastitis prior to FPAI (2.0 ± 0.1 and 106.2 ± 4.8 d, respectively) and those that had no mastitis or had mastitis after pregnancy confirmation (1.6 ± 0.2 and 85.4 ± 5.8 d, respectively), respectively. Similarly to the study by Barker et al. (1998), the correlation between mastitis and reproductive efficiency was not dependent on type of bacteria isolated from milk samples.

In a large study performed in the Central Valley of California (Santos et al., 2004), 1,001 lactating Holstein cows from two dairy herds were also classified according to the timing of occurrence of the first mastitis case during the lactation as: no clinical mastitis (CON), mastitis occurring before FPAI (MG1), mastitis occurring between FPAI and pregnancy diagnosis (MG2), or mastitis occurring after pregnancy confirmation (MG3). Cows were followed during the first 320 DIM and reproductive performance was evaluated. The conception rates (CR) after FPAI and the proportion of cows pregnant after 320 DIM were significantly smaller for MG1

and MG2 cows compared with CON and MG3 cows (Figure 1). Cows in the MG2 group had the greatest SPC compared with the other three groups (CON = 2.59 ± 0.10 , MG1 = 2.62 ± 0.14 , MG2 = 3.05 ± 0.20 , MG3 = 2.47 ± 0.17). Furthermore, cows that experienced mastitis, regardless of timing of the event, had increased incidence of abortion between 42 ± 7 and 180 ± 14 d after AI (Figure 1). Cows in the MG1 and MG2 groups had extended interval from calving to conception compared with CON and MG3 cows (CON = 139.7 ± 3.7 , MG1 = 165.0 ± 5.7 , MG2 = 189.4 ± 6.4 , and MG3 = 118.4 ± 6.4 d). When cows were grouped as either not experiencing mastitis (CON) or experiencing mastitis (MG1, MG2, and MG3), those that experienced mastitis had longer interval from calving to conception (Figure 2). Similarly to the studies by Barker et al. (1998) and Schrick et al. (2001), the type of bacteria responsible for the mastitis event did not affect the correlation between mastitis and reproductive performance.

Chebel et al. (2004) evaluated factors that affect conception rates (CR) and pregnancy loss in lactating Holstein cows from three different dairy herds in the Central Valley of California. In this study a total of 7,633 AI were used for evaluation of factors affecting CR and 1,465 cows diagnosed pregnant by ultrasonography at 31 d after AI and re-examined 14 d later were used for evaluation of factors affecting pregnancy loss. Among the factors evaluated was occurrence of mastitis between AI and pregnancy confirmation at approximately 45 d after AI. Cows that experienced mastitis during this interval had similar conception rates (24.0%) compared with those cows that did not experience mastitis (25.5%). However, when cows had mastitis between AI and pregnancy confirmation they were 2.80 times more likely to experience pregnancy loss between 31 and 45 d after AI compared with those cows that did not have mastitis (Figure 3). In a subsequent study, the same group evaluated the correlation between subclinical mastitis and pregnancy maintenance (Moore et al., 2005). Cows were classified as experiencing subclinical mastitis when they had LSCC > 4.5 in the test day immediately prior to the AI but had no clinical signs of mastitis (Moore et al., 2005). Pregnancy was diagnosed at 28 d after AI by ultrasonography and at 35 d after AI by palpation per rectum. Cows classified as experiencing subclinical mastitis immediately prior to AI were 2.40 times more likely to lose the pregnancy between 28 and 35 d after AI compared with those cows that had LSCC ≤ 4.5 (Figure 3).

In another large study, McDougall et al. (2005) evaluated the reproductive performance of 2,004 lactating cows from 10 pasture-fed dairy herds in New Zealand. Cows that had received FPAI within 16 d after the initiation of the breeding season were examined for pregnancy status 29-45 d after AI and at 6, 8, 10, 14, and 22 weeks of gestation. Cows were followed during the entire lactation. In this study, the risk for pregnancy loss was 1.57 times greater for cows that experienced mastitis at any time during the lactation compared with those that never experienced mastitis (Figure 4).

From the data presented above it is clear that there is a correlation between mastitis and fertility. These findings have led to the hypothesis that the inflammatory and immune responses to the IMI affect reproductive performance by preventing ovulation and resumption of cyclicity after calving (i.e. extended calving to FPAI interval), by reducing fertilization rates and embryo development (i.e. reduced CR and increased SPC), and by compromising embryonic development and pregnancy establishment and maintenance (i.e. reduced embryonic/fetal survival and increased incidence of abortions). It is important to note, however, that it is not possible to rule out the possibility that cows that are prone to developing mastitis are more

debilitated and consequently more prone to develop reproductive disorders that may ultimately affect their fertility.

Mechanisms by which Mastitis May Affect Fertility

One of the possible mechanisms for the reduction in fertility of lactating dairy cows that develop mastitis is the elevated body temperature (pyrexia or fever), which can result from both gram-positive and gram-negative infections of the mammary gland (Wenz et al., 2001). *In vitro* studies have demonstrated that smaller proportion of oocytes and embryos cultured under heat stress develop to the blastocyst stage (Edwards and Hansen, 1997; Krininger et al., 2002). Furthermore, when lactating dairy cows and dairy heifers were exposed to heat stress, the fertilization rate and the proportion of excellent/good quality embryos were dramatically smaller for lactating dairy cows compared to heifers (Sartori et al., 2003). This indicates that exposure of oocytes and embryos to heat stress compromises fertilization and development. Aside the direct effect of elevated body temperature on oocyte and embryo quality and development, fever can indirectly affect reproductive performance because cows that experience it have decreased feed intake and body condition (Maltz et al., 1997). Therefore, if a cow develops mastitis and fever during early postpartum, a period of the lactation in which cows are already predisposed to reduced feed intake, greater loss of body condition and more pronounced negative energy balance may occur, which could delay resumption of ovarian cyclicity (Buttler, 2000).

Another possible mechanism by which mastitis may affect fertility in lactating dairy cows is through the production of substances that affect oocyte and embryo quality and development, uterine environment, and ovarian function. These substances are called cytokines and among them interleukin (IL)-1 α , IL-1 β , IL-6, IL-10, IL-12, and tumor necrosis factor- α (TNF- α) have been isolated from milk-derived cells from infected mammary glands (Riollet et al., 2001). Furthermore, challenge of lactating cows with components of the cell wall (lypopolysaccharide, LPS) of *Escherichia coli* (gram-negative bacteria) resulted in increased milk concentrations of IL-1 β , IL-8, and TNF- α (Blum et al., 2000; Waller et al., 2003). Other studies have also demonstrated that cows that experience mastitis have increased blood concentrations of TNF- α , IL-1, and IL-6 (Hoeben et al., 2000; Nakajima et al., 1997). Mastitis is also correlated with increased concentrations of nitric oxide (NO) and prostaglandin F2 α (PGF2 α) in milk and mastitic cows challenged with oxytocin had increased blood concentrations of PGF2 α metabolite (Blum et al., 2000; Bouchard et al., 1999; Giri et al., 1984; Hockett et al., 2000). These findings indicate that infections of the mammary gland may result in a systemic response with the production of compounds that may disturb fertility.

Oocyte and Embryo Development and Uterine Environment

Most of the studies conducted to evaluate the effects of the compounds produced because of IMI on oocyte and embryo development were based on *in vitro* models, which means that studies were not conducted in live animals. Although results from *in vitro* studies not always are observed *in vivo*, they provide insightful information about possible mechanisms by which mastitis may affect fertility.

Maturation of bovine oocytes in the presence of TNF- α resulted in reduced proportion of fertilized oocytes developing to the blastocyst stage (Soto et al., 2003). Furthermore, embryos

cultured in the presence of TNF- α , PGF2 α , or NO had either increased number of apoptotic cells (dead cells) or compromised development to the blastocyst stage (Pampfer et al., 1994; Wu et al., 1999; Soto et al., 2003; Chen et al., 2001; Hobbs et al., 1999). Furthermore, administration of PGF2 α to cows supplemented with progesterone resulted in poorer quality embryos and decreased pregnancy rates, reinforcing the idea that PGF2 α may have a direct effect on embryo development (Buford et al., 1996).

Prostaglandin F2 α produced by the endometrium (one of the layers of the uterine wall) is also responsible for luteolysis, which occurs at the end of the estrous cycle if an embryo is not present. It has been demonstrated that production of PGF2 α can be stimulated by cytokines such as TNF- β and IL-1c (Skarzynski et al., 2000; Davidson et al., 1995). Therefore, mastitis can lead to an increase in secretion of PGF2 α and consequently premature luteolysis, which could result in embryonic/fetal death.

Although it is not clear whether mastitis could increase the production of compounds such as TNF- α , PGF2 α , and NO in the reproductive tract, this is possible because the production of these compounds is systemically stimulated by cytokines.

Hypothalamic-Pituitary-Ovarian Axis

Reproductive cycles in cows are regulated by hormones produced in the hypothalamus (GnRH = gonadotropin releasing hormone) and pituitary (FSH = follicle stimulating hormone and LH = luteinizing hormone), which are glands located in the brain, and ovaries (E2 = estradiol and P4 = progesterone). Briefly, GnRH is responsible for stimulating the secretion of FSH and LH. Follicle stimulating hormone is responsible for stimulating initial growth of follicles in the ovaries, while LH is responsible for maturation of follicles and ovulation and also for stimulation of P4 secretion by the corpus luteum. Estradiol, produced by the follicles, is responsible for stimulating the peak of LH that causes ovulation, while P4 is responsible for stimulating embryo growth and maintenance of pregnancy. Therefore, it is clear that the disruption of production or secretion of one of these hormones may dramatically affect the fertility of dairy cows.

It has been demonstrated that certain cytokines such as IFN- β decrease the secretion of LH (McCann et al., 2000). Furthermore, mastitis and exposure of cows to endotoxins secreted by gram-negative bacteria result in increased blood concentrations of cortisol, a hormone that blocks the release and the peak of LH (Stoebel et al., 1982; Li et al., 1983; Padmanabhan et al., 1983). The decrease or lack of LH secretion may result in compromised follicle and oocyte development, lack of ovulation, and suboptimal luteal function. Some of the cytokines produced during mastitis also have a direct effect on the ovaries. Interleukin-6, for example, blocks the secretion of estradiol (Alpizar et al., 1994), which can lead to reduced LH secretion, while TNF- β and IFN- δ are cytotoxic to the corpus luteum (Fairchild et al., 1991; Petroff et al., 2001) and could cause reduction in concentrations of P4.

Conclusions

It is clear that a correlation between mastitis and reproductive failure exist. Reproductive performance of lactating dairy cows that experience mastitis could be affected in many ways. The longer interval from calving to first postpartum AI could be the result of extended period of

anovulation following calving caused by reduced energy balance as a consequence of fever or blockage of GnRH-LH secretion. Production of poorer quality oocytes or embryos because of exposure to fever or to compounds that are deleterious to their development could be manifested by reduced conception rates and increased services per conception. Finally, longer interval from calving to conception could be the result of the conditions mentioned above and increased embryonic/fetal loss or abortions. Therefore, the appropriate management of lactating dairy cows to minimize the incidence of mastitis should increase the profitability of dairy herds not only by improving milk quality, reducing the use of antibiotics, reducing the amount of milk discarded, and reducing involuntary culling but also by improving reproductive performance.

References

- Alpizar, E., and L.J. Spicer. 1994. Effects of interleukin-6 on proliferation and follicle-stimulating hormone-induced estradiol production by bovine granulosa cells in vitro: dependence on size of follicle. *Biol. Reprod.* 50: 38.
- Barker, A.R., F.N. Schrick, M.J. Lewis, H.H. Dowlen, and S.P. Oliver. 1998. Influence of Clinical Mastitis During Early Lactation on Reproductive Performance of Jersey Cows. *J. Dairy Sci.* 81:1285.
- Blum, J.W., H. Dosogne, D. Hoeben, F. Vangroenweghe, H.M. Hammon, R.M. Bruckmaier, C. Burvenich. 2000. Tumor necrosis factor- β and nitrite/nitrate responses during acute mastitis induced by *Escherichia coli* infection and endotoxin in dairy cows. *Dom. Anim. Endocrinol.* 19: 223.
- Bouchard, L., S. Blais, C. Desrosiers, X. Zhao, and P. Lacasse. 1999. Nitric oxide production during endotoxin-induced mastitis in the cow. *J. Dairy Sci.* 82: 2574.
- Buford, W.I., N. Ahmad, F.N. Schrick, R.L. Butcher, P.E. Lewis, and E.K. Inskeep. 1996. Embryotoxicity of a regressing corpus luteum in beef cows supplemented with progesterone. *Biol. Reprod.* 54: 351.
- Buttler, W.R. 2000. Nutritional interactions with reproductive performance in dairy cattle. *Anim. Reprod. Sci.* 60: 449.
- Chebel, R.C., J.E.P. Santos, J.P. Reynolds, R.L.A. Cerri, S.O. Juchem, and M. Overton. 2004. Factors affecting conception rate after artificial insemination and pregnancy loss in lactating dairy cows. *Anim. Reprod. Sci.* 84: 239.
- Chen, H.W., W.S. Jiang, and C.R. Tzeng. 2001. Nitric oxide as a regulator in preimplantation embryo development and apoptosis. *Fertil. Steril.* 75: 1163.
- Davidson, J.A., U. Tiemann, J.G. Betts, and P.J. Hansen. 1995. DNA synthesis and prostaglandin secretion by bovine endometrial cells as regulated by interleukin-1. *Reprod. Fertil. Dev.* 7: 1037.
- Edwards, J.L., and P.J. Hansen. 1997. Differential responses of bovine oocytes and preimplantation embryos to heat shock. *Mol. Reprod. Dev.* 46: 138.

- Fairchild, D.L., and J.L. Pate. 1991. Modulation of bovine luteal cell synthetic capacity by interferon-d. *Biol. Reprod.* 44: 357.
- Giri, S.N., Z. Chen, E.J. Carroll, R. Mueller, M.J. Schiedt, and L. Panico. 1984. Role of prostaglandins in pathogenesis of bovine mastitis induced by *Escherichia coli* endotoxin. *Am. J. Vet. Res.* 45: 586.
- Hansen, P.J., P. Soto, and R.P. Natzke. 2004. Mastitis and fertility in cattle – Possible involvement of inflammation or immune activation in embryonic mortality. *Am. J. Reprod. Immunol.* 51: 294.
- Hockett, M.E., F.M. Hopkins, M.J. Lewis, A.M. Saxton, H.H. Dowlen, S.P. Oliver, and F.N. Schrick. 2000. Endocrine profiles of dairy cows following experimentally induced clinical mastitis during early lactation. *Anim. Reprod. Sci.* 58:241.
- Hoeben, D., C. Burvenich, E. Trevisi, G. Bertoni, J. Hamann, R.M. Bruckmaier, and J.W. Blum. 2000. Role of endotoxin and TNF- β in the pathogenesis of experimentally induced coliform mastitis in periparturient cows. *J. Dairy Res.* 67: 503.
- Hobbs, A.J., A. Higgs, and S. Moncada. 1999. Inhibition of nitric oxide synthase as potential therapeutic target. *Annu. Rev. Pharmacol. Toxicol.* 39: 191.
- Krinninger, C.E. III, S.H. Stephens, and P.J. Hansen. 2002. Developmental changes in inhibitory effects of arsenic and heat shock on growth of preimplantation bovine embryos. *Mol. Reprod. Dev.* 63: 335.
- Li, P.S., and W.C. Wagner. 1983. In vivo and in vitro studies on the effect of adrenocorticotrophic hormone or cortisol on the pituitary response to gonadotropin releasing hormone. *Biol. Reprod.* 29: 25.
- Maltz, E., S. Devir, J.H.M. Metz, H. Hogeveen. 1997. The body weight of the dairy cow. I. Introductory study into body weight changes in dairy cows as a management aid. *Livest. Prod. Sci.* 48: 175.
- McCann, S.M., M. Kimura, S. Karanth, W.H. Yu, C.A. Mastronardi, and V. Rettori. 2000. The mechanism of action of cytokines to control the release of hypothalamic and pituitary hormones in infection. *Ann. N. Y. Acad. Sci.* 917: 4.
- McDougall, S., F.M. Rhodes, and G.A. Verkerk. 2005. Pregnancy loss in dairy cattle in the Waikato region of New Zealand. *N. Z. Vet. J.* 53: 279.
- Moore, D.A., J.S. Cullor, R.H. Bondurant, and W.M. Sisco. 1991. Preliminary field evidence for the association of clinical mastitis with altered interestrus intervals in dairy cattle. *Theriogenology* 36: 257.
- Moore, D.A., M.W. Overton, R.C. Chebel, M.L. Truscott, and R.H. BonDurant. 2005. Evaluation of factors that affect embryonic loss in dairy cattle. *J. Am. Vet. Med. Assoc.* 226: 1112.

- Nakajima, Y., O. Mikami, M. Yoshioka, Y. Motoi, T. Ito, Y. Ishikawa, M. Fuse, K. Nakano, and K. Yasukawa. 1997. Elevated levels of tumor necrosis factor-b (TNF-b) and interleukin-6 (IL-6) activities in the sera and milk of cows with naturally occurring coliform mastitis. *Res. Vet. Sci.* 62: 297.
- Padmanabhan, V., C. Keech, and E.M. Convey. 1983. Cortisol inhibits and adrenocorticotropin has no effect on luteinizing hormone-releasing hormone-induced release of luteinizing hormone from bovine pituitary cells in vitro. *Endocrinology* 112: 1782.
- Pampfer, S., Y.D. Wu, I. Vanderheyden, and R. De Hertogh. 1994. Expression of tumor necrosis factor-b (TNF-b) receptors and selective effect of TNFb on the inner cell mass in mouse blastocyst. *Endocrinology* 134: 206.
- Petroff, M.G., B.K. Petroff, and J.L. Pate. 2001. Mechanisms of cytokine-induced death of cultured bovine luteal cells. *Reproduction* 121:753.
- Riollet, C., P. Rainard, B. Poutrel. 2001. Cell subpopulations and cytokine expression in cow milk in response to chronic *Staphylococcus aureus* infection. *J. Dairy Sci.* 84: 1077.
- Santos, J.E.P., R.L.A. Cerri, M.A. Ballou, G.E. Higginbotham, and J.H. Kirk. 2004. Effect of timing of first clinical mastitis occurrence on lactational and reproductive performance of Holstein dairy cows. *Anim. Repro. Sci.* 80: 31.
- Sartori, R., R. Sartor-Bergfeldt, S.A. Mertens, J.N. Guenther, J.J. Parrish, and M.C. Wiltbank. 2002. Fertilization and Early Embryonic Development in Heifers and Lactating Cows in Summer and Lactating and Dry Cows in Winter. *J. Dairy Sci.* 85: 2803.
- Schrick, F.N., M.E. Hockett, A.M. Saxton, M.J. Lewis, H.H. Dowlen, and S.P. Oliver. 2001. Influence of Subclinical Mastitis During Early Lactation on Reproductive Parameters. *J. Dairy Sci.* 84: 1407.
- Skarzynski, D.J., Y. Miyamoto, and K. Okuda. 2000. Production of prostaglandin F 2b by cultured bovine endometrial cells in response to tumor necrosis factor b: cell type specificity and intracellular mechanisms. *Biol. Reprod.* 62: 1116.
- Soto, P., R.P. Natzke, and P.J. Hansen. 2003. Actions of tumor necrosis factor-b on oocyte maturation and embryonic development in cattle. *Am. J. Reprod. Immunol.* 50: 380.
- Soto, P., R.P. Natzke, and P.J. Hansen. 2003. Identification of possible mediators of embryonic mortality cause by mastitis: actions of lipopolysaccharide, prostaglandin F_{2α}, and the nitric oxide generator, sodium nitroprusside dihydrate, on oocyte maturation and embryonic development in cattle. *Am. J. Reprod. Immunol.* 50: 263.
- Stoebel, D.P., and G.P. Moberg. 1982. Effect of adrenocorticotropin and cortisol on luteinizing hormone surge and estrous behavior of cows. *J. Dairy Sci.* 65: 1016.
- Waller, K.P., I.G. Colditz, K. Östensson. 2003. Cytokines in mammary lymph and milk during endotoxin-induced bovine mastitis. *Res. Vet. Sci.* 74: 31.

Wenz, J.R., G.M. Barrington, F.B. Garry, K.D. McSweeney, R.P. Dinsmore, G. Goodell, and R.J. Callan. 2001. Bacteremia associated with naturally occurring acute coliform mastitis dairy cows. *J. Am. Vet. Med. Assoc.* 219: 976.

Wuu, Y.D., S. Pampfer, P. Becquet, I. Vanderheyden, K.H. Lee, and R. De Hertogh. 1999. Tumor necrosis factor b decreases the viability of mouse blastocyst in vitro and in vivo. *Biol. Reprod.* 60: 479.

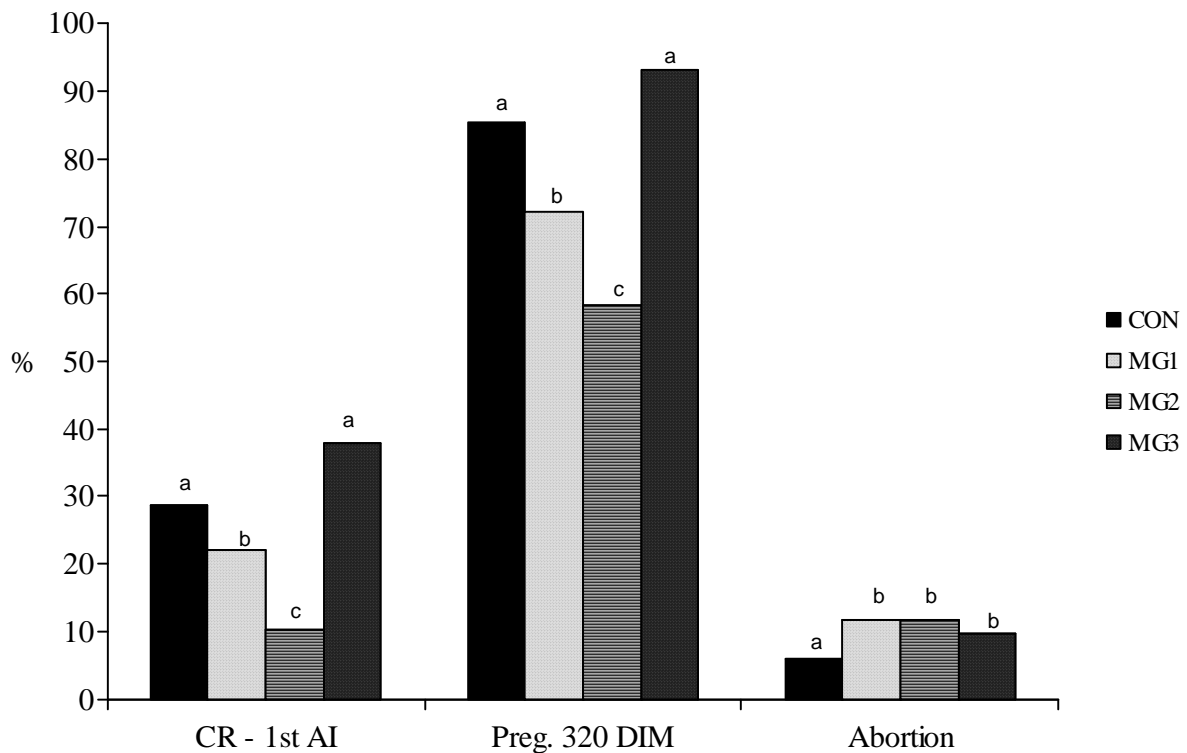


Figure 1 – Correlation between mastitis and conception rate after 1st postpartum AI (CR – 1st AI), proportion of cows pregnant after 320 DIM (Preg. 320 DIM), and incidence of abortions (Abortion) in Holstein cows. CON = no mastitis; MG1 = mastitis occurred before FPAI; MG2 = mastitis occurred between FPAI and pregnancy diagnosis; and MG3 = mastitis occurred after pregnancy confirmation. Proportions with different superscript within study differ ($P < 0.05$). Adapted from Santos et al. (2004).

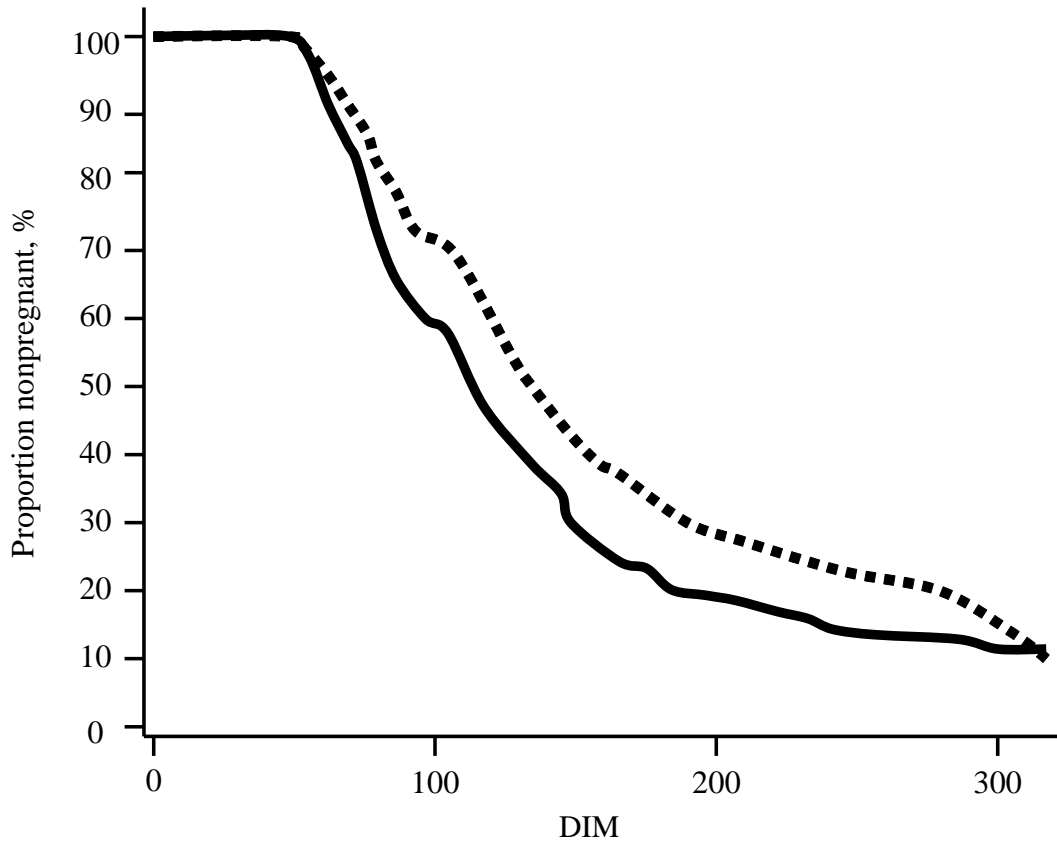


Figure 2 – Correlation between occurrence of mastitis and speed at which Holstein cows became pregnant. Cows that did not experience mastitis are represented by the solid line and cows that experienced mastitis are represented by the dotted line. Adapted from Santos et al. (2004).

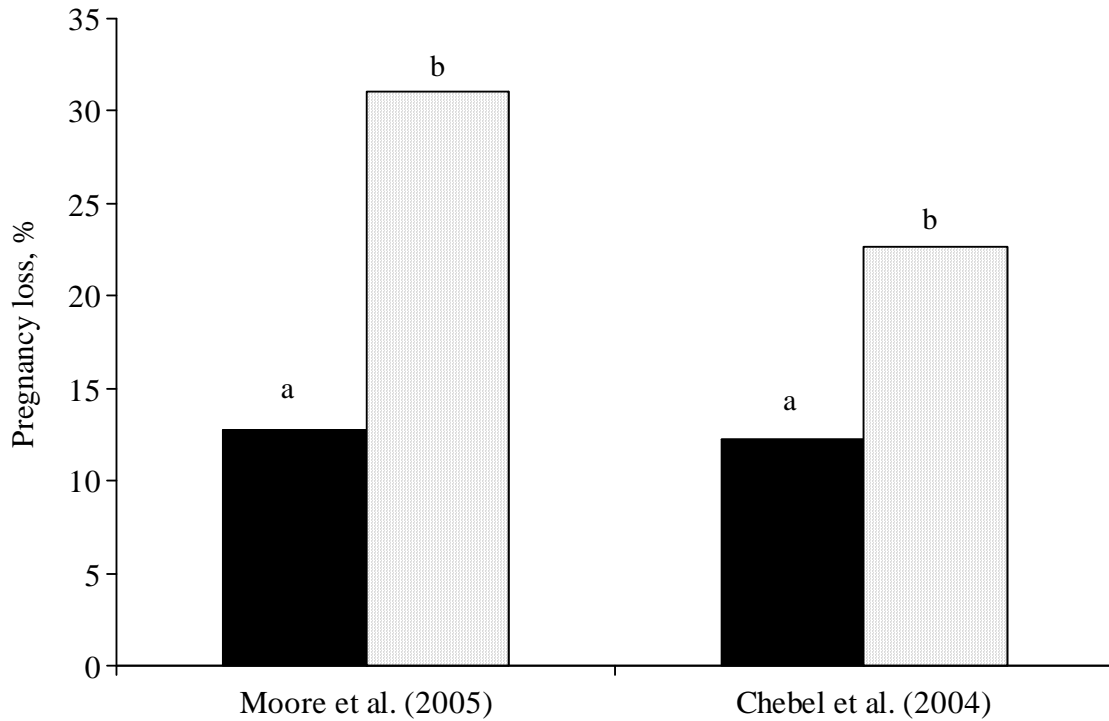


Figure 3 – Correlation between subclinical mastitis [no mastitis = $LSCC \leq 4.5$ (solid bar); subclinical mastitis = $LSCC > 4.5$ (dashed bar)] and pregnancy loss from 28 to 35 d after AI [Moore et al. (2005)] and between clinical mastitis (no mastitis = solid bar and clinical mastitis = dashed bar) and pregnancy loss from 31 to 45 d after AI [Chebel et al. (2004)]. Proportions with different superscript within study differ ($P < 0.05$).

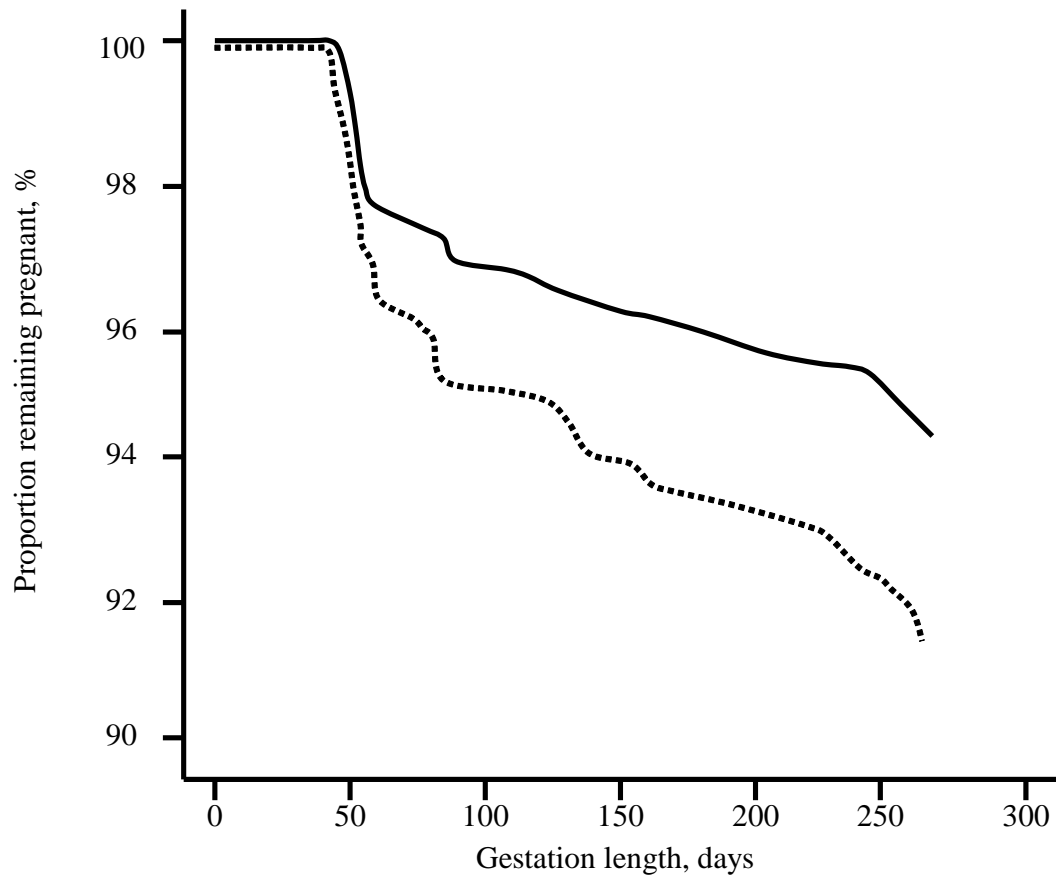


Figure 4 – Survival analysis of cows remaining pregnant. Solid line represents cows that did not experience mastitis and dotted line represents cows that experienced mastitis. Adapted from McDougall et al. (2005).

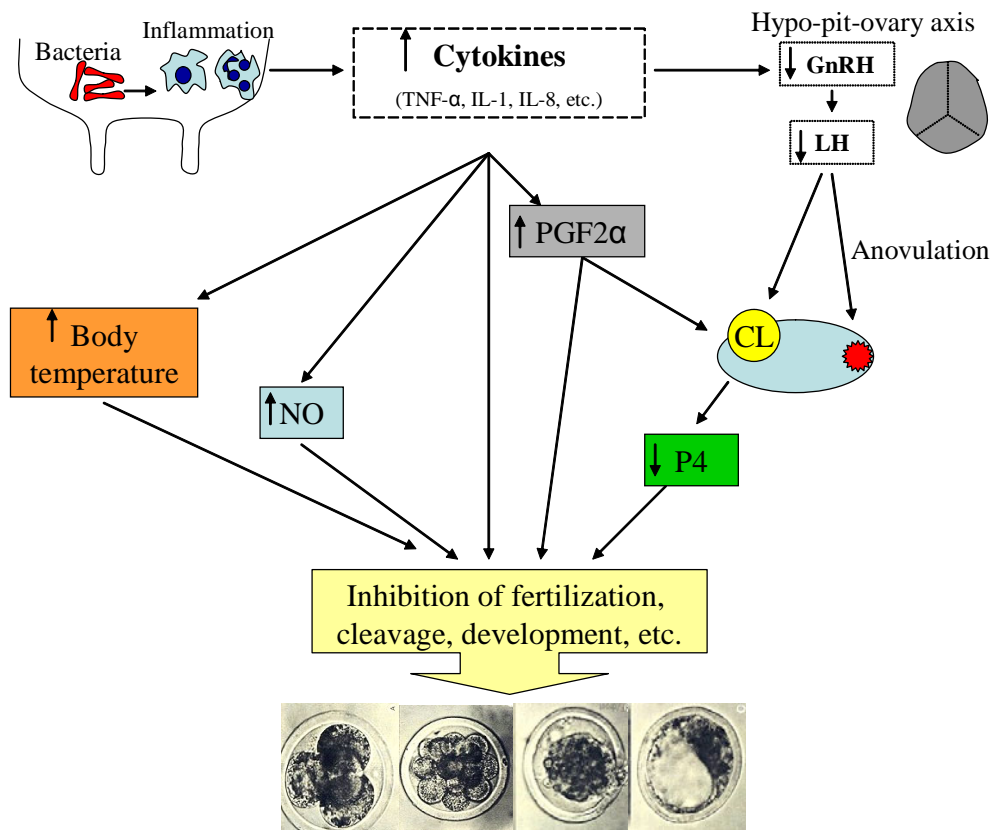


Figure 5 – Hypothetical model by which mastitis affects fertility in lactating dairy cows. Adapted from Hansen et al. (2004).