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Impact of Mastitis on Reproductive Performance in Dairy Animals: A Review

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ABSTRACT

In present scenario the two most common diseases complexes affecting the dairy cattle worldwide are mastitis and infertility, since both are multifactorial in origin, they increase the culling rate and loss in the profitability of a farm. Other than being a trending animal welfare issue, it has a grave effect on quantity and quality of milk. The reproductive performance of dairy animals is influenced by several factors, and various evidences indicate that mastitis is one of the determinants. The multifaceted nature of both mastitis and reproduction makes it difficult to understand their relationship in detail, thus only a retrospective approach is appraised rather than a controlled clinical study. Thus in this review, information regarding the effects of clinical mastitis on reproductive function and the most probable mechanisms by which mastitis affects reproduction in dairy animals is explained.

Keywords: Mastitis, infertility, reproductive performance

The fate of the newly formed embryo is unknown. It is estimated that about 50% of human embryos are lost before implantation (Kline, 1989). In dairy cattle, pregnancy rate has been decreasing over the last 30 years. Pregnancy rates of 50–60% in the 1970s have declined drastically to values of 35–45% today. Reproductive efficiency is one of the most important determinants of profitability in dairying. Over decades, reproductive efficiency in dairy cattle has declined across the world (Lucy, 2001). Though there are several causes but infertility due to peri- and postpartum complications is a well-known factor for reduced reproductive efficiency. The mechanisms that cause embryo survival and death are not completely understood. Recent, studies in cattle have led to the evolution of the idea that infectious disease outside the reproductive tract can lead to reduced pregnancy rate. The relationship between mastitis and reproduction has been retrospectively reported by several authors (Barker *et al.,* 1998; Gunay and Gunay, 2008). Current information indicate that mastitis causes decreased pregnancy rates, aberrations in the estrous cycle (Moore *et al.,* 1991), early embryonic mortality or abortions (Risco *et al.,* 1999), prolonged days open (Barker *et al.,* 1998; Gunay and Gunay 2008), higher number of services per conception, and decreased conception rate (Kelton *et al.,* 2001; Hertl *et al.,* 2010) in dairy cattle. However, controlled clinical studies on understanding the pathogenesis of mastitis on reproduction are limited. The present review furnishes the available information on the effects of mastitis on reproduction and attempts to explain the possible mechanisms by which mastitis influences reproductive performance in dairy animals.

Effect of Mastitis on Reproductive Functions

Mastitis is an inflammation of the mammary gland caused in cattle primarily by bacteria. Clinical symptoms include, altered milk composition and appearance, decreased milk production, increased numbers of leukocytes in milk, increased body temperature, and red, warm, and swollen mammary quarters. The first study to suggest a relationship between mastitis and fertility was carried out by Barker *et al.* in 1998 involving a comparison of reproductive records between 102 lactating Jersey cows suffering from clinical mastitis with that of 103 lactating Jersey cows without mastitis (Barker *et al.,* 1998).

As per the information available, it indicates that mastitis leads to decreased pregnancy rates, aberrations in the estrous cycle (Moore *et al.,* 1991), early embryonic mortality or abortions (Risco *et al.,* 1999), prolonged days open (Barker *et al.,*1998; Gunay and Gunay 2008), higher number of services per conception, and decreased conception rate (Kelton *et al.,* 2001; Hertl *et al.,* 2010) in dairy cattle. And amongst these services per conception has been observed at higher incidence associated with either anovulation at estrus, fertilization failure or embryonic mortality. Mastitis in its subclinical form disrupts the functioning of the preovulatory follicle, resulting in low fertility. A major cause of this disruption is delayed ovulation associated with low follicular steroid production in about one-third of subclinical mastitic cows; the remaining two-thirds respond normally (Wolfenson *et al.,* 2015). Poor reproductive performance in mastitis-affected cows could be due to altered hormonal profile, oocyte competence, fertilization failure, and unfavorable uterine environment for embryonic development. Although the causes of early embryonic loss after fertilization or before implantation are multifactorial, few studies indicated that infectious disease or activation of immune responses elsewhere in the body (outside of the reproductive tract) might have an impact on the survival of early embryo.

Critical period in which mastitis adversely affects reproduction

The period of occurrence of mastitis influences the intensity of adverse effects on postpartum reproduction in cows. Barker *et al.* (1998) and Schrick *et al.* (2001) investigated the effect clinical mastitis during different times and found that clinical mastitis before AI increased the number of days to first AI, while clinical mastitis after first AI increased days open (DO) and service index (number of AI required per conception). It was concluded that clinical mastitis during early lactation had a negative impact on the reproductive performance of dairy cows. In contrast Gómez-Cifuentes *et al.* (2014) found no association between time of occurrence of clinical mastitis and pregnancy rate or number of services per conception. Boujenane *et al.* (2015) reported that when clinical mastitis was considered as fixed effect, it had significant effects on days to first service, while nonsignificant effects were observed on DO and service index. However, when it was classified based on the time of first clinical mastitis occurrence (<60, 60–90, and >90 DIM), there was no significant effect on reproductive performance. Podpečan *et al.* (2013) reported that mastitic cows in the first 3 months postpartum did not differ significantly from the clinically healthy cows in terms of days to first service, first service to conception interval, and days open.

Hockett *et al.* (2005) reported that cows with clinical mastitis during preovulatory period had decreased expression of estrus, period of estrus, and pregnancy rate. Further, to understand its mechanism, *Str. Uberis* induced mastitis before ovulation was used to study the effects on endocrine profile and ovarian structure and found that estradiol remained at basal levels in cows following experimentally induced clinical mastitis along with reduced LH pulsatality and LH surge, without affecting the follicle size. It ultimately decreased the estrous behavior and delayed establishment of pregnancy for approximately one estrus cycle.

On other hand, the occurrence of mastitis after ovulation had minimal effects on reproductive performance. In contrast, induction of mastitis during the luteal phase of early lactation (≈30 DIM), the cows (3–4 days after induction) had more concentration of cortisol on the 4th and 7th days, while the peak concentration of PGFM (after oxytocin challenge) was also increased in mastitic than control cows. However, no differences were found in the concentration of prolactin, LH (after GnRH challenge), and estradiol between mastitis and control cows (Hockett *et al.*, 2000). These contrasting results clearly indicates the role of physiological status of the animals and the importance of proper experimental design to understand the effects of mastitis on reproduction

Possible mechanisms by which mastitis affects reproduction

Decreased reproductive performance in mastitis-affected cows could be due to altered oocyte competence, fertilization failure, hormonal profile, and unfavorable uterine environment for embryonic development. Though the causes of early embryonic loss after fertilization or before implantation are multifactorial, few studies indicated that infectious disease or activation of immune responses elsewhere in the body (outside of the reproductive tract) might have an impact on the survival of early embryo. For instance, in response to the anecdotal statement of bovine practitioners about the relationship between clinical mastitis and pregnancy rate, a preliminary study by Cullor (1990) revealed an disrupted interestrus interval (less than 18 days or more than 24 days) in clinical mastitis cows; however, the effects varied with mastitis pathogen and age of the animal (Moore *et al.*, 1991). It was suggested that endotoxin might induce luteolysis through the release of prostaglandin F2α (PGF2α) and other inflammatory mediators thus affecting early embryonic survival (Moore and Connor 1993). The possible mechanism by which mastitis affects reproduction is explained in Fig. 1.

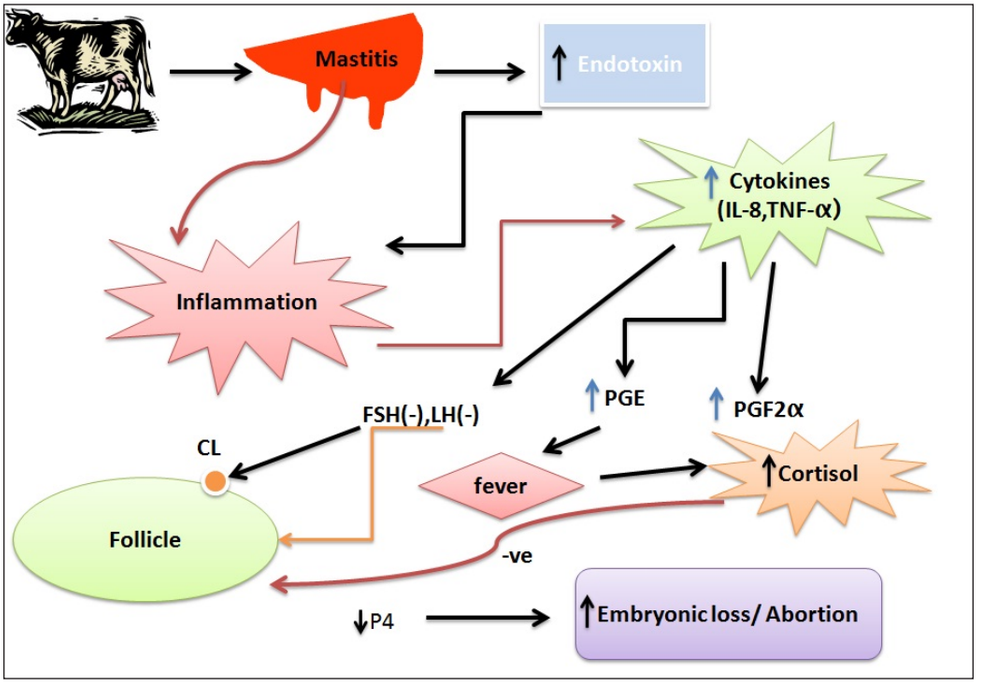

Fig. 1: Possible mechanism by which mastitis affects the reproductive functions in the mastitis

Hyperthermia and Pregnancy rate

There are a number of possible mechanisms by which mastitis could negatively affect fertility. One mechanism is that the elevation in body temperature in mastitis compromises reproductive processes. It is a well-known fact that heat stress has compromising effect on fertility. One of the effect of heat stress on embryonic survival is because of the direct effects of elevated temperature on oocyte and embryo function as culture of maturing oocytes (Edwards *et al.,* 1997) or pre-implantation embryos (Edwards *et al.,* 1997; Krininger *et al.*, 2002) reduced development to the blastocyst stage suggestive of that elevated body temperature may directly alter the developmental competence of oocyte and embryo or indirectly affect reproductive performance through decreased feed intake and body condition (Maltz *et al.,* 1997). It also appears that oocyte competence can be compromised by heat stress during follicular development. Heat stress ten days before estrus reduced pregnancy rate in sheep (Dutt, 1963). Bovine oocytes collected during warm weather have reduced ability to yield blastocysts when subjected to in vitro fertilization. (Rutledge *et al.,* 1999; Al-katanani *et al.,* 2002).

Inflammatory Mediatorism as Disruptors of Oocyte Maturation and Embryonic Development

Mastitis leads to production of a various bioactive molecules that can potentially disrupt reproductive tract tissues. Nakajima *et al.* (1997) found higher levels of tumor necrosis factor (TNF)-α and interleukin (IL)-6 in the serum and milk of cows affected with coliform mastitis and suggested that these cytokines might play an important role in inducing udder inflammation. Waller *et al.* (2003) explored the kinetics of neutrophils, cytokines (IL-8, TNF-α, IL-1β), and interferon-γ in milk and lymph of the supramammary lymph node after intramammary infusion of endotoxin and found that IL-8 plays a major role in the recruitment of neutrophils into the mammary gland. Experimental treatment with LPS increased peripheral blood concentrations of TNF-α (Steiger *et al.,* 1999; Perkins *et al.,* 2001). Mastitis and LPS infusion is also associated with increased synthesis of molecules whose production can be activated by specific cytokines. In particular, mastitis and endotoxin treatment increased concentrations of nitric oxide (NO) in milk (Bouchard *et al.,* 1990) and intramammary injection of *E. coli* endotoxin resulted in increased milk concentrations of prostaglandin F2α (PGF2α) (Giri *et al.,* 1984). It has also been documented (Hockett *et al.,* 2000) that cows with mastitis had a higher peak concentration of 13, 14-dihydro-15-keto PGF2α (the major PGF2α metabolite, PGFM) in blood following oxytocin challenge compared with control cows.

Out of these molecules, TNF-α, NO, and PGF2α act either on the oocyte or on the developing embryo thereby affect embryonic development. Addition of TNF-α to bovine oocytes matured in vitro did not alter subsequent cleavage when oocytes were fertilized but the proportion of oocytes that became blastocyts was reduced when TNF-α is added to bovine embryos after fertilization, increasing the proportion of blastomeres becoming apoptotic. TNF-α when overexpressed leads to embryonic apoptosis resulting in embryonic death in diabetic rats (Pampfer, 2001).

Prostaglandin F2α has a negative effect on embryo development in cattle: administration of PGF2α to cows receiving supplemental progesterone compromised embryonic development and decreased pregnancy rate (Buford *et al.,* 1996). Increased concentrations of NO have also been associated with early embryonic death. Culture with sodium nitroprusside dihydrate, a NO donor, prevented development to the blastocyst stage of bovine (Lim *et al.,* 1998) and mouse embryos (Chen *et al.,* 2001) The toxic effects of NO may occur through interaction between NO and O_{2^-} to form the oxidant peroxynitrite. Soto *et al.* in 2003 found out on experimentation that

the concentration of LPS required to interfere with oocyte function was too high (1 ng/mL), which is irrelevant to the situation in mastitis and even higher concentrations (1000 ng/mL) of LPS had no effect on blastocyst development when added to the embryo culture after fertilization. Thus, the major reproduction-disrupting role that LPS plays during mastitis is to trigger release of cytokines and other molecules that interfere with reproduction and not to directly interfere with oocyte and embryo function.

Disruption of the Hypothalamic– Pituitary– Ovarian Axis

One probable reason for increased number of services per conception in cows with mastitis is due inhibition of gonadotropin secretion leading to reduced gonadotropin support for, folliculogenesis, ovulation, oocyte maturation and luteal function. Certain cytokines can decrease LH release (McCann *et al.,* 2000). In an epidemiological survey carried by Wolfenson *et al.* in 2015 suggested that clinical mastitis was associated with activation of the glucocorticoid system, resulting in a sharp rise of systemic cortisol, known to be involved in depression of gonadotropin-releasing hormone (GnRH) and LH secretion (Lavon *et al.*, 2010) exhibiting delayed ovulation that is caused by low secretion of estradiol and a low or delayed preovulatory LH surge. Low estradiol in the circulation close to estrus is associated with disruption of its positive effect on GnRH secretion, consequently leading to disruption of normal secretion of the preovulatory LH surge.

In cattle, for example, IFN-α secretion of LH can also be blocked by cortisol (Padmanaban *et al.,* 1983) a hormone whose secretion can be elevated during mastitis or after endotoxin treatment (Peter *et al.,* 1984). Cytokines released during mastitis can also have direct effects on the ovary. IL-6 blocks follicle stimulating hormone-induced estradiol secretion from bovine granulosa cells, especially from cells isolated from small follicles (Alpizar *et al.,* 1994) Both TNF-*a* and IFN-c are cytotoxic to bovine luteal cells.

Non-specific Effects of Mastitis on Reproduction

The major drawbacks in the evaluation of reproductive performance in mastitis-affected cows are due to difficulties in understanding all possible confounding factors responsible for the relationship between mastitis and fertility. For instance, decreased reproductive performance of an individual animal (Nebel and McGilliard 1993) may be associated with either mastitis or higher milk production (Windig *et al.,* 2005). Therefore, studying the influence of mastitis on reproductive performance in cows with different capacities of milk production and under different management systems besides the prevailing agri-ecological conditions assumes significance. Further, advanced statistical models to handle these confounding factors are important to improve the statistical output and discuss about the problem. Since the relationship between mastitis and reproduction was initially through retrospective studies (Barker *et al.,* 1998; Santos *et al.,* 2004), the possibility of other diseases in these clinical mastitis cows cannot be ruled out. Several other authors (Loeffler *et al.,* 1999; Maizon *et al.,* 2004) also reported that, other than mastitis, dystocia, displaced abomasums, RP, milk fever (MF), ketosis, metritis (ME), and pyometra negatively influenced the reproductive performance of dairy cows. Vacek *et al.* (2007) evaluated the relationship among several health disorders (milk fever, metritis, endometritis and pyometra, OC, and lameness) including clinical mastitis and reproductive performance in dairy cows. They found that RP, OC, and MEhad a significant effect on the days to first AI, days open, and service per conception (SC), while MF delayed days to first AI and lameness increased days open and SC. However, the relationship between CM and fertility parameters was not as explicit as the authors found that CM only increased days open and days to first service, without altering other fertility parameters.

Ribeiro *et al.* (2013) reported that clinical and subclinical periparturient diseases showed an additive negative effect on reproduction. However, individually, mastitis did not alter the resumption of estrous cyclicity and pregnancy per AI on day 30 and day 65 after insemination in these cows. In contrast, Peake *et al.* (2011) reported that the combined incidence of lameness, subclinical mastitis, and body condition score loss causes delayed onset of first luteal phase from calving and had synergistic detrimental effects on progesterone profile in Holstein-Friesian cows.

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