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IMPACT OF SUBCLINICAL MASTITIS ON REPRODUCTIVE PERFORMANCE OF DAIRY ANIMALS

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ABSTRACT

According to the international dairy federation, the dairy sector provides up to one billion livelihoods around the globe. Albeit, it faces many challenges including the two potentially threatening diseases which are mastitis and infertility. Both are complex multifactorial diseases, and mastitis is associated with causing infertility. Mastitis is an intramammary infection (IMI) and it occurs in two forms, clinical and subclinical. Mastitis being the infection of mammary glands, directly affects milk production to reduce its quality and quantity and indirectly hinders the reproductive performance of dairy animals. It negatively affects the reproduction parameters of dairy animals including, an increase in days open, a decrease in pregnancy rates, and increases chances of early embryonic losses and abortion. The chronic cases of mastitis lead toward the infertility of dairy animals and both of these diseases are responsible for increasing the culling rate and decreasing the profitability of a dairy farm. The objective of this study is to illustrate the influence of subclinical mastitis on reproduction parameters of dairy animals including, days open, days to the first service after calving, pregnancy rates, abortion, and embryonic losses. The relation between mastitis and infertility will be explained mechanistically.

Contribution/Originality: This study contributes to the literature related to the field of animal science and particularly it discusses the issues related to subclinical mastitis in dairy animals. The primary purpose of this study is to bring this issue under the attention of animal science researchers and veterinarians to understand the gravity of situation and to work for treatment and cure of intramammary infections.

1. INTRODUCTION

The importance of dairy can be understood from the fact that people of every country across the globe milk dairy animals and up to one billion people live on dairy farms (https://www.fil-idf.org/). But the dairy sector faces many challenges including the challenge of mastitis which leads towards infertility in chronic cases. In dairy cattle, pregnancy rates are decreasing from last few decades. Pregnancy rates from 50–60% in the 1970s have declined drastically to values of 35–45% in the recent past [1, 2].

Mastitis is described as the infection of mammary glands which causes physical, chemical and bacteriological changes in milk and pathological changes in mammary glands [3]. Intramammary infection (IMI) happened to be the most common problem in dairy animals [4] thus, causing significant economic losses and is also a reason for antibiotic resistance in animals and humans [5-7]. Subclinical mastitis (SCM) is one of the two forms of mastitis in which clinical signs do not appear thus, it is also known as asymptomatic inflammation of mammary tissue [8]. This form of mastitis has 15-40% more chances to occur [9] because of its asymptomatic nature. SCM is diagnosed through somatic cell count SCC of milk sample and in SCM the somatic cell count is about 200000 cells/ml in bovine [10] which is positive in milk samples three to four times per year [11].

Dairy herd efficiency is measured through the amount of milk sold per cow per day of life. The primary determinant of dairy herd efficiency and profitability is reproductive performance because of its associations with the milk production, culling rate, cost of breeding, and the number of calves born per year [12]. There are many factors affecting dairy herd efficiency, but reproductive performance is a significant shareholder which is negatively affected by mastitis [13]. Mastitis causes extensive economic losses in cattle dairy farms through its treatment costs, replacement of early culled animals and decreased production losses [14, 15] which causes the ineffective use of inputs ending up in increased per unit production of greenhouse gas emissions [16]. Mastitis in dairy animals is much devastating as it decreases milk production directly but also has an indirect impact on the reproductive efficiency [17] of the animals, such as the reduction in the number of calves born per year [10]. It also increases the days to the first service, decreases the conception rate and also increases the number of abortions [18]. For maintenance and sustainability of a farm to be economical the optimization of reproductive efficiency is the need of the time [19]. During the last few decades measures were taken to control mastitis which were fruitful to some extent, but subclinical mastitis is a challenging issue hitherto [20].

In this review, we will elaborate about the effects of SCM on the reproductive performance of animals. The mechanism through which SCM effects the reproductive parameters will also be discussed.

2. SUBCLINICAL MASTITIS AND FERTILITY OF DAIRY ANIMALS

2.1. Contribution of Oxidative Stress Caused by IMI to Infertility

The mammalian life needs oxygen for its oxidative metabolism which provides energy. During oxidative metabolism, some reactive oxygen species (ROS) are produced as a by-product which are neutralized by antioxidant mechanisms under physiological conditions [21]. However, during pathological conditions, the ROS production increases significantly which may exceed the protective mechanisms capacity and therefore can cause tissue damage. Conditions like inflammation which are meant to eliminate the noxious agent and to repair the tissue damage result in oxidative stress and excessive ROS production [22]. The oxidative stress and excessive ROS productions cause damage to the oocytes. For example, during prophase of meiosis I, it results in incorrect chromosome segregation [23]. The chronic cases of inflammation during postpartum time could cause the oxidative stress to a certain level which imposes damage to the resting as well as developing oocytes. It also affects DNA and because of that the fertility of animals is diminished [24].

Oxidative stress caused by IMI can cause direct insults to oocytes, it also results in impaired granulosa cell function which ends up with indirect wearying of functional oocytes. The oxidative stress to oocytes recovered along with granulosa cells for human *in vitro* fertilization (IVF) resulted in failed fertilization [25]. This evidence reveals that oxidative damage to the antral follicle causes potential damage to the oocyte [26].

2.2. Effect of IMI on the Primordial Follicle Pool

Primordial follicles are the reserve pool for the production of oocytes in animals after the start of puberty until death. Chronic Inflammation and its associated oxidative stress are the main contributors to infertility through oocyte damage. However, the inflammation and oxidative stress can also deplete the reserve primordial follicles

through their premature activation. Because, once the follicles are activated, then they are destined to develop until ovulation or atresia [26].

The acute loss of primordial follicles was observed after the *in vitro* administration of lipopolysaccharides (LPS) to the bovine ovarian cortex. The inflammatory processes activated the phosphoinositol 3 kinase (PI3K) which converts the phosphoinositol diphosphate to phosphoinositol triphosphate, along with activation of protein kinase B (PKB). The activation of this pathway results in stimulation of the primordial follicle which leaves their resting pool and gets on board for development to ovulation or atresia [27]. Thus, in this way, the depletion of primordial follicles not just cuts short the reproductive lifespan, but also affects the fertility during normal reproductive stages of dairy animals [28]. The number of antral follicles is an indicator of healthy follicles and oocytes. The fertility in cows with a higher number of antral follicles is higher than those with a lower number of antral follicles [29, 30]. Thus, the inflammatory mediated depletion of primordial follicles can have a permanently deleterious effect on the fertility of dairy animals.

2.3. Impact of IMI on the Consequent Failure of Fertilization

The bacterial toxins and the inflammatory mediators can travel to the follicular environment through general circulation. Endotoxins can be found in the ovarian tissue after the intramammary infection in animals [31]. The endotoxin in ovarian tissue exerts a detrimental effect on the competence of oocytes [32].

The expression of Toll-like receptors (TLR) by granulosa and theca cells makes them responsive to LPS and other bacterial products [31-33]. The activation of TLRs on granulosa and theca cells disturbs the communication between oocyte and cumulus cells that is needed for the development of competent oocyte [34].

Thus, the subclinical mastitis leads towards infertility through premature activation of primordial follicles, infliction of insults to developing oocytes through oxidative stress, and through disruption of communication between oocytes and cumulus cells.

3. MASTITIS IMPACT ON CONCEPTION RATE, PREGNANCY RATE AND DAYS OPEN

Conception rate is the detection of positive early days pregnancy compared to the number of artificial inseminations, and pregnancy rate is the percentage of attempts to get animals pregnant. Days open is calving to conception period of animals.

Subclinical mastitis interferes with intake, partition, and expenditure of nutrients and energy which results in mobilization of body reserves, lowering body condition and delaying the postpartum resumption of the estrous cycle [35]. Decreased body condition comes up with a reduction in the fertility of dairy cows [36]. Therefore, delayed first breeding postpartum causes reproductive inefficiency and economic losses Ribeiro, et al. [37]. Santos, et al. [38] studied the relation of ovulation and the number of viable oocytes and the number of viable oocytes was lower in subclinical mastitis as it causes the degeneration of oocytes. Intra-mammary infections promote delayed ovulation and alter the functionality of corpus luteum (CL) formed after the ovulation [38]. Either clinical or subclinical IMI caused by gram-positive or gram-negative bacteria pre or post insemination drops the conception rate [34]. In chronic cases of subclinical mastitis 30 percent of affected cows showed delayed ovulation [39]. Moreover, exposure of cows to endotoxin during estrus triggered a diminished and delayed luteinizing hormone (LH) surge in one-third of the cows which resulted in delayed ovulation and, ultimately, decreased the chances of successful fertilization [39].

These shreds of evidence show that intramammary infection causes delayed ovulation which results in increased days open. It also affects the competence of oocyte through oxidative stress, inflammatory mediators and decreased body condition which results in lowered conception and pregnancy rates in dairy animals.

Furthermore, Schrick, et al. [40] reported the effects of IMI on reproductive parameters of animals at different time periods of their reproductive cycles Figure 1 and the SC mastitis which occurred between first insemination and pregnancy had the most deleterious effects [40].

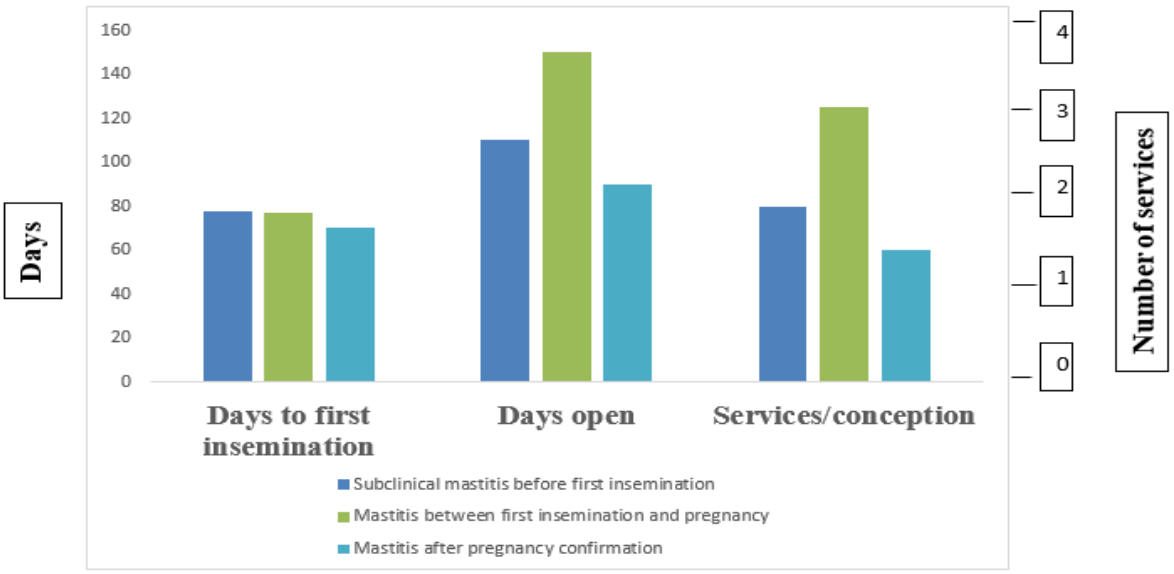

Figure-1. Effects of mastitis occurred at different times on days to the first insemination, days open, and services per conception.
Source: Modified from Schrick, et al. [40].

4. PROPOSED MECHANISMS WHICH DISTURBS THE CONCEPTION AND PREGNANCY RATES

4.1. Mastitis Mediated Mechanisms which Effects Steroidogenesis

In the limelight of the relation of subclinical mastitis and fertility, the possible mechanism which affects conception rate and maintenance of pregnancy will be demonstrated here. The immediate impact of subclinical mastitis regarding reproductive performance is the disruption of the endocrine mechanism associated with androgens. Shortly, the inflammation mediators and bacterial endotoxins released through induction of mastitis such as cytokines, interleukins, and prostaglandin F2α (PGF2 α) affect the endocrine pathways related to reproduction [18]. This causes the disturbance in hypothalamo-pituitary-ovarian-uterine axis [41] which results in altered reproductive parameters of cows, causing anestrous, anovulation and infertility. Further, the cows affected with the subclinical or clinical disease showed delayed estrous cycle resumption which prolongs the period between calving and first service [36, 42].

Besides, the likely reason behind delayed ovulation is reduced estradiol production which is due to the stimulation of TLR receptors on theca cells by inflammatory products and mediators [31, 33, 43]. The dropped amount of estrogen in circulation results in dim and delayed preovulatory LH surge which subsequently causes delayed ovulation. In their study, Magata, et al. [33] cultured bovine theca cells *in vitro* in a media containing peptidoglycan and/or LPS to investigate the effects of these bacterial toxins on steroidogenesis. Theca cells presented TLR receptors and nucleotide-binding oligomerization domain 1 and 2. The bacterial toxins caused decreased prostaglandin and androstenedione production along with decreased mRNA expression of steroidogenic enzymes. These findings show that bacterial toxins directly affect the steroidogenesis in theca cells which results in poor growth of oocytes [44]. In another study, Lavon, et al. [45] revealed that 33% of the cows affected with naturally occurring subclinical mastitis showed decreased follicular androstenedione, and decreased mRNA expression of genes associated with steroidogenesis in both granulosa and theca cell layers [45] might be because of oxidative stress. The decrease in follicular estradiol concentrations two weeks after G+ or G- toxin exposure disturbed the functioning of small follicles during folliculogenesis and damaged preovulatory follicles as well [46]. Additionally, shreds of evidence from previous studies have also shown that follicular growth halts in mastitis

effected cows [31, 34], possibly because of decreased LH concentrations, as the administration of *E. coli* endotoxins through intramammary infusion decreased the LH pulsatility which altered the development of preovulatory follicles [47, 48]. The follicular growth was also reduced in animals with continuous infusion of *Staph. aureus* toxin for three weeks [46]. Thus, intra-mammary infections could promote delayed or absence of ovulation [39] which causes decreased fertility or infertility in dairy animals.

The reduction in the follicular concentration of estradiol in granulosa cells of the ovary and of androstenedione in theca cells is associated with a decrease in expression of steroidogenic enzymes and LH receptor (LHR) in granulosa and theca cells [49]. In a concordant study, Magata, et al. [33] showed that low concentrations of LPS in follicular fluid suppresses the transcription of steroidogenic enzymes including CYP17 and P450 [44]. Another similar study conducted by Lavon, et al. [50] showed a similar mechanism of abnormally low expression of LHR and steroidogenic genes in both granulosa and theca cells [50]. Gloominess in estradiol levels in follicles of subclinically affected mastitis animals was caused by reduced CYP10A expression in granulosa cells [50].

Therefore, the negative effects of IMI on the production of the androgen impairs the normal regulation of oocyte development and ovulation which is reason for decreased conception and pregnancy rates and increased days open in mastitis affected animals.

4.2. Disruption of the Hypothalamic-Pituitary-Ovarian Axis

A plausible reason for an increase in the number of services per conception in cows with mastitis is hang-up of gonadotropic release which reduces follicle growth, ovulation, and functioning of corpus luteum [1]. The IMI relates to stimulation of the glucocorticoid system [49] coming up with a sharp rise of systemic cortisol, which is involved in the depression of gonadotropin-releasing hormone (GnRH) and LH secretion ,therefore, orchestrating the delayed ovulation [45]. This disturbance in hypothalamo-pituitary-ovarian-uterian axis [41] alters the reproductive parameters of cows, causing anestrous, anovulation and infertility. Low level of estradiol in blood near to estrus is associated with a disturbance of its positive effect on GnRH secretion, consequently leading to interruption of the normal flow of the preovulatory LH surge. Insignificant reproductive performance in mastitis-affected cows could be linked to the altered hormonal profile, fertilization failure, and unfavorable uterine milieu for embryonic development [1].

The graphical presentation of the proposed mechanism for the influence of IMI on reproductive parameters is given in Figure 2.

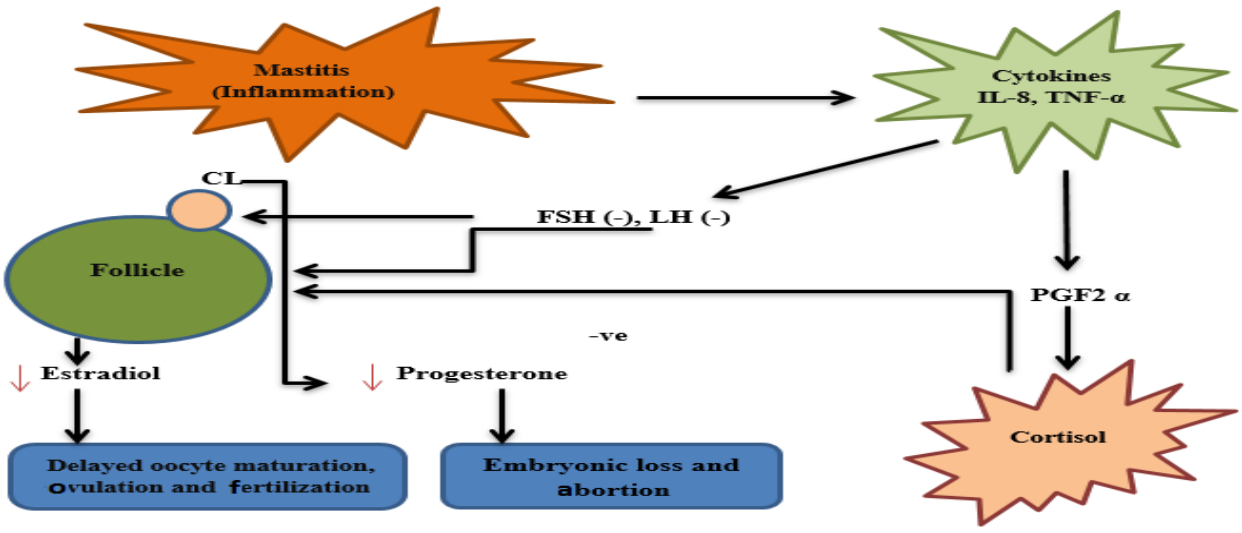

Figure-2. Shows potential effects of mastitis on follicle growth, ovulation, CL, and pregnancy maintenance through negative feedback of inflammatory mediators and their positive feedback on cortisol. The negative feedback of cortisol on FSH and LH also elaborates on the decrease in estradiol and progesterone concentrations and their ultimate consequences.

Source: Modified from Sharma, et al. [1].

5. MASTITIS VERSUS EARLY EMBRYONIC LOSSES AND ABORTION

The early embryonic loss is a loss of embryo before 45 days and abortion is termed as the loss of a fetus after 45 days of pregnancy. The odds of pregnancy loss (PL) are 1.2 times higher in cows affected with subclinical mastitis during the first 90 days of gestation as compared to cows without subclinical mastitis [9]. The inflammation due to mastitis not only causes the impaired oocyte development and incompetence of oocyte but also causes the impaired development of morula and further development of conceptus to elongation stages which, sometimes, results in early embryonic loss or abortion [35]. Moreover, endotoxins were found to be associated with inhibition of meiotic progression in bovine oocytes. Further, the LPS exposure to bovine oocytes also decreased the mitochondrial membrane potential and halted the redistribution of mitochondria all over the cytoplasm. Further, the oocytes matured in LPS exposure showed a significantly lower number of trophoblasts. These results indicate that endotoxin exposure leads to the impaired nuclear and cytoplasmic maturation of oocytes and also disturbs the subsequent embryonic development [32]. Those cows which have subclinical mastitis show decidedly fewer pregnancy rates and those cows which have subclinical mastitis after service to 30 days indicate more infrequent pregnancy rates. The root of this effect is the release of PGF2 alpha which causes premature luteolysis and the ultimate decrease in the pregnancy rates. The embryonic mortality is due to the activation of inflammatory and immune responses. These responses occur due to the release of lipopolysaccharides from bacteria entered to mammary glands [3].

Recently, Mohsen, et al. [3] investigated the relevance between animals of subclinical and clinical mastitis to pregnancy rate and embryonic loss percentage [3]. They found that the percentage of pregnancy rate (44.45%) was lower in SC mastitis affected animals as compared to normal ones (60.87%) but it was higher than the clinical mastitis affected animals (16%). While the embryonic loss percentage showed that SC mastitis animals had higher (11.11%) than the normal (8.70%) but lower than clinical mastitis animals [3]. This data clearly tells us that subclinical mastitis drops down the pregnancy rate and increases the embryonic losses rate of dairy animals which turns out to be a huge loss in terms of economics.

The biggest hurdle in developing the direct and authentic relation between mastitis and PL [51] is less information about the compounding factors involved in this disease [1, 52]. However, the pieces of evidence we have discussed above are the indicators for the impact of subclinical mastitis on the reproductive parameters of dairy animals. Research is needed (1) for livelihood of the hypothesis that mastitis in combination with low BCS or other factors can increase the risk of PL, (2) to link the effect of mastitis before and during gestation on PL, and (3) to associate the impact of mastitis on PL in dairy cows during different lactations [53].

6. CONCLUSORY REMARKS AND RECOMMENDATIONS

In sum, we have learned that subclinical mastitis has negative impacts on the reproductive parameters of dairy animals. These negative impacts are mediated by a different mechanism including oxidative stress, depletion of primordial follicle pool, decrease in oocyte competence, decreased steroidogenesis, and delayed ovulation. These perturbed reproductive parameters lead to the increased days open, decreased conception rates, and improper development or loss of the fetus. The ultimate impact of subclinical mastitis is on the economic efficiency of the dairy herd through its treatment costs, replacement of prematurely culled animals, and production losses.

According to FAO and OECD, the consumption of dairy products is expected to increase by 20% or more before 2021. In this context, it is the utmost need of time to set proper checks for control of subclinical and clinical mastitis in order to improve the production of high-quality milk and to improve the reproductive efficiency of dairy animals. As the global human population is increasing the requirements of the availability of milk and meat will be met if these two interlinked complex diseases are controlled. The first step in controlling the subclinical mastitis is its early diagnosis which is very difficult to handle through conventional methods. Thus, the use of newly developed

tools such as infrared thermometers and dynamometers can aid in early diagnosis of subclinical mastitis. Measures for the prevention of subclinical mastitis through the management and use of vaccinations should be promoted.

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