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Evidence that mastitis can cause pregnancy loss in dairy cows: A systematic review of observational studies

Mohammad O. Dahl,*† Fiona P. Maunsell,* Albert De Vries,‡ Klibs N. Galvao,*§ Carlos A. Risco,* and Jorge A. Hernandez*[1]
*Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville 32611-0910
†Department of Medicine and Preventive Medicine, College of Veterinary Medicine, University of Mosul, Mosul, Iraq 41002
‡Department of Animal Sciences, College of Agriculture and Life Sciences, University of Florida, Gainesville 32611-0910
§D. H. Barron Reproductive and Perinatal Biology Research Program, University of Florida, Gainesville 32610

ABSTRACT

The objective of this study was to conduct a systematic review to identify and assess evidence and knowledge gaps in published observational studies that have investigated the relationship between mastitis and pregnancy loss (PL) in dairy cows. PubMed and ScienceDirect were used to search pertinent peer-reviewed research reports of interest. Screening of research reports was conducted at 3 levels: titles, abstracts, and full-text articles. The search identified 651 records for initial screening. The final screening process identified 8 qualified articles for review after removing 10 duplicate records, 582 titles, 31 abstracts, and 20 full-text articles. Two studies produced strong epidemiologic evidence indicating that (1) exposure to clinical mastitis during early gestation (first 45 d of gestation) is associated with subsequent PL during the following 90 d; and (2) subclinical mastitis 1 to 30 d before artificial insemination (AI) is associated with subsequent PL at 35 to 41 d of gestation. An additional study showed that exposure to clinical mastitis during early lactation in combination with low body condition can increase the risk of PL in dairy cows; however, the interaction effect between clinical mastitis and low body condition on PL was considered weak. Four other studies produced inconclusive evidence indicating that mastitis is a predisposing factor for PL in dairy cows, as the exposure risk period for mastitis overlapped with the follow-up period for diagnosis of PL in dairy cows. Finally, one study failed to identify a relationship between mastitis and PL in dairy cows. Further research is needed to (1) support the hypothesis that mastitis in combination with low body condition score (or other exposure factors) can increase the risk of PL, (2) compare the effect of clinical versus subclinical mastitis on PL, (3) compare the effect of mastitis before breeding and during gestation on PL, and (4) compare the effect of mastitis on PL in dairy cows during different lactations.
Key words: pregnancy loss, mastitis, dairy, systematic review

INTRODUCTION

Pregnancy loss (**PL**) has been defined as the loss of pregnancy in cows that were first confirmed pregnant at about 30 to 50 d after AI and later exhibited visual signs of abortion or were declared not pregnant during reconfirmation of pregnancy (Risco et al., 1999; Chebel et al., 2004; Moore et al., 2005). Pregnancy loss impairs reproductive performance in dairy cows, thus affecting the profitability of dairy farms. Economic losses due to PL have ranged between $555 and $2,333 as a result of repeat breeding, extended calving interval, labor and medical costs, decreased milk yield, and culling of dairy cows (De Vries, 2006; Lee and Kim, 2007). In the United States, prevalence of PL in dairy cows has varied from 6 to 39% (Risco et al., 1999; Chebel et al., 2004; Moore et al., 2005).

Embryonic mortality and PL can be linked to mastitis as a function of endotoxins or inflammatory and immune responses. Inducing clinical mastitis with *Escherichia coli*, *Klebsiella pneumonia*, or *Streptococcus uberis* in dairy cows increased SCC in milk (Paape et al., 2002; Persson Waller et al., 2003), the concentration of $PGF_{2\alpha}$ in milk and plasma (Cullor, 1990; Hockett et al., 2000), and the activity of pro-inflammatory cytokines, particularly tumor necrosis factor (TNF)-α, IL-1β, and IL-8 in milk, lymph, and blood (Shuster et al., 1993; Rainard and Paape, 1997; Hoeben et al., 2000; Paape et al., 2002; Persson Waller et al., 2003; Rambeaud et al., 2003). Cytokines have cytotoxic activity on the corpus luteum (Schams and Berisha, 2004) and can increase $PGF_{2\alpha}$ concentration (Townson

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[1]Corresponding author: hernandezja@ufl.edu

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and Pate, 1994), resulting in luteolysis and termination of pregnancy. Endotoxins and cytokines (TNF-α) can impair early embryonic development, affecting embryo survival (Soto et al., 2003; Hansen et al., 2004).

Several observational studies have reported that clinical or subclinical mastitis is a predisposing factor for PL in dairy cows (Risco et al., 1999; Chebel et al., 2004; Santos et al., 2004; McDougall et al., 2005; Moore et al., 2005; Pinedo et al., 2009; Hernandez et al., 2012). In 2 studies, the odds of PL were 2.7 or 2.8 times higher in cows affected with clinical mastitis during early gestation compared with cows without clinical mastitis (Risco et al., 1999; Chebel et al., 2004). In 2 other studies, exposure to clinical mastitis any time during lactation was associated with an increased risk of PL in dairy cows (Santos et al., 2004; McDougall et al., 2005). In 2 additional studies, the odds of PL were >3.5 times higher in cows affected with subclinical mastitis before gestation (Moore et al., 2005) or 1.2 times higher in cows with subclinical mastitis during early gestation (Pinedo et al., 2009) compared with cows without mastitis. A seventh study identified an interaction effect between clinical mastitis during early lactation and low body condition at 70 DIM on PL in dairy cows (Hernandez et al., 2012). Finally, a study by López-Gatius et al. (2002) failed to identify a relationship between clinical mastitis and PL in dairy cows during the first 38 to 90 d of gestation. Although published observational studies have provided different levels of evidence indicating that mastitis can cause PL in dairy cows, most of these studies used nonobjective research methods and failed to establish a temporal relationship between mastitis and PL in dairy cows, making their study results inconclusive. To our knowledge, a systematic review that has carefully examined the evidence of association between mastitis and PL in dairy cows produced by observational studies has not been published. Therefore, our objective was to conduct a systematic review to identify and assess the evidence and knowledge gaps in published observational studies that have investigated the relationship between mastitis and PL in dairy cows.

MATERIALS AND METHODS

A systematic review for epidemiologic studies that examined mastitis as a predisposing factor for PL in dairy cows was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). In this study, PL was defined as cows that were declared pregnant at about d 30 after AI and later exhibited visual signs of abortion or were diagnosed as not pregnant via ultrasound or rectal palpation.

Eligibility Criteria

Observational studies written in English that presented original data and were published in peer-reviewed journals were considered for inclusion. Narrative reviews, meta-analyses, or studies published only as abstracts were excluded. Characteristics of studies included in this review were identified according to the PICOS approach (P: population; I: intervention (or exposures); C: comparators; O: outcome; and S: study designs; Liberati et al., 2009) and included (1) study population: dairy cows during different parities from dairy herds inside or outside the United States; (2) exposure of interest: clinical or subclinical mastitis, provided that clinical mastitis was diagnosed by detecting abnormal changes in the milk or udder, and subclinical mastitis was identified by applying diagnostic tests to the milk, such as SCC, assuming that cows with mastitis were identified equally accurately in all studies; (3) comparators: dairy cows that had not been exposed to clinical or subclinical mastitis; (4) outcome of interest: PL, which was identified as declared pregnant cows that exhibited visual signs of abortion or were diagnosed not pregnant during second or later pregnancy diagnosis, where first pregnancy diagnosis in commercial herds is usually performed around d 30 after AI; and (5) study design: observational studies targeted examining the association between PL and exposure to mastitis alone or in combination with other exposure factor(s).

Information Sources and Selection Process

Two online search engines, PubMed and ScienceDirect, identified as high-quality scientific search engines (Samadzadeh et al., 2013) were used to track pertinent peer-reviewed research reports. The search was initially conducted on February 21, 2014, and then updated on April 3, 2016. Keywords used were mastitis, pregnancy, abortion, dairy, cow, and cattle. Selected keywords were entered in the search box as a phrase where each word was followed by comma and one space as follows: "mastitis, pregnancy, abortion, dairy, cow, cattle". The PubMed database was selected from "database selection menu" located on the left of the search box on PubMed's home page display (https://www.ncbi.nlm.nih.gov/pubmed). In addition, no filters were applied in either PubMed or ScienceDirect. Duplicate records from both PubMed and ScienceDirect were excluded. Screening was conducted at 3 levels: titles, abstracts,

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