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PATHOGENESIS, TREATMENT AND CONTROL OF BOVINE CLINICAL ENDOMETRITIS: A REVIEW

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ABSTRACT

Clinical endometritis is a common uterine disease of bovine caused by various pathogenic bacteria, owing to reduce the reproductive efficiency, infertility and huge economic losses to the livestock farmer. It has already been reported that endometritis affects reproductive performance of livestock by delaying service interval, reduce conception rate, and repeat breeding. Contamination during artificial insemination, dystocia, unhygienic handling of parturition, multiple birth and abortion are the predisposing factors related to endometritis in cattle. Additionally, several microorganisms have been frequently isolated such as *Escherichia coli, Fusobacterium necrophorum, Actinomyces pyogenes* and *Bacteroides* species. Due to lack of awareness regarding the diagnosis and treatment of this devastating condition, farmers usually cull exaggerated animals even having better genetic potential. The present review summarizes the contemporary understanding about the quantifiable importance of endometritis, including aetiology, clinical signs, diagnosis, treatment and its control. Moreover, present work will researchers, veterinarians and dairy farmers in early diagnosis and treatment this menace to minimize economic losses and also safeguard high milk yielding animal.

Keywords: bovine, clinical endometritis, control, pathogenesis, treatment

INTRODUCTION

Reproductive health is one of the key pillars in production of herd and individual animal. In the female animals, the reproductive health could be affected by uterine infections such as endometritis and metritis that inflict huge economic impact on the productivity of an animal. Endometritis is the inflammation of the functional epithelial lining of uterus and most prevalent pathological condition in cattle in Pakistan. It is characterized by the presence of a muco-purulent discharge, detectable in vagina from 21 to 26 days postpartum (Iain Martin Sheldon *et al.,* 2009. Endometritis affects the inner layer of uterus (endometrium), specifically the epithelium, stromal cells, gland necks of stratus compactum, stroma and gland bodies of stratum spongiosum exclusive of any systemic infection (Azawi and Azar, 2002; Azawi *et al.*, 2008a). Moreover, impact of endometritis on bovine reproductive health is shown in Figure 1.

Several postpartum disorders are interlinked and might have a common etiology. Amongst, endometritis, metritis, pyometra and retention of fetal membrane (RFM) are significant pathological disorders responsible for infertility in high yield cattle in dairy industries (Deori and Phookan, 2015). Interestingly, these undesired conditions have frequent etiological agents, thus therapeutic regime applied are common and effective (Deori and Phookan, 2015). In fact, in most of the cases, low fertility has also been reported in dairy cattle due to endometritis (Gautam *et al.*, 2009). However, microbial infections have been reported in infertility associated to disruption of uterus and ovaries during or immediate after parturition. Conversely, other predisposing factors responsible might be twins, dystocia, stillbirths, male offspring, abortion, retained fetal membranes, ketosis, and metritis (Galvão *et al.*, 2009; Dubuc *et al.*, 2010; Potter *et al.*, 2010; Cheong *et al.*, 2011). In Pakistan, endometritis is frequent cause of infertility and repeat breeding due to unhygienic handling of parturition, dystocia and artificial insemination. Many farmers cull their animals due to lack of comprehensive understanding of clinical endometritis and its treatment.

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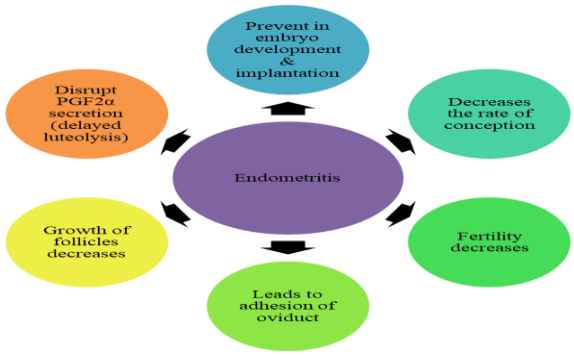

Figure 1. Effects of endometritis in bovine reproductive health

Significance of endometritis

Uterine infection restricts involution process and consequently leads to infertility through deteriorating ovarian functions. A variety of factors are held responsible for economic losses such as systemic illness, decreased milk and meat production and low fertility (Deori and Phookan, 2015). Clinical endometritis can cause increased service interval, decreased rate of conception, delayed ovulation, luteolysis and early embryonic death.

Prevalence

In the northern part of Pakistan, the incidence rate of endometritis was recorded as 4% in Achai cattle, which is lowest percentage than other cattle breeds (Sohail *et al.*, 2018) and around 40% animals develop metritis (uterine infection) within the first week of calving. Out of 40%, 10 to 15% carry endometritis (Sheldon and Dobson, 2004). In addition, the prevalence of postpartum endometritis in Sahiwal cattle was reported as 2.8% in District Faisalabad (Khan *et al.*, 2020). Overall, worldwide incidence rate of postpartum endometritis cases ranges between 7 to 18%, (Martinez and Thibier, 1984).

Aetiology of clinical endometritis

After parturition, 90% of cows are infected with uterine infection due to a variety of bacterial and fungal organisms (Azawi *et al.*, 2008b; Khan *et al.*, 2008). Bacterial infection can cause clinical endometritis in 15 to 20% of postpartum dairy cows and reduce their fertility, even after resolution of this condition. Hence, the most significant pathologic agents are *Actinomyces pyogenes, Corynebacterium puedotuberculosis, Leptospira, Brucella abortus, Camphylobacter fetus, Trichomonas fetus, E. coli, Bacteriode spp., fusobacterium necrophorum* and *Clostridrium* spp. Furthermore, most of the infected animals with systemic illness show decreased milk yield, dullness, and or other signs of toxemia (Sheldon *et al.*, 2006).

Whereas, various pathogens have been isolated from severe endometritis associated with *Actinomyces pyogenes* after 21 days of postpartum (Griffin *et al.*, 1974; Hussain *et al.*, 1990). Moreover, significant role of Gram -ve anaerobic bacteria associated with *Actinomyces pyogenes* in field study has also been confirmed (Noakes *et al.*, 1989; Noakes *et al.*, 1990). And microbial synergism has been found between *A. pyogenes* and *Fusobacterium necrophorum* (Ruder *et al.*, 1981) and between *A. pyogenes*, *F. necrophorum* and *Bacteroides melaninogenicus* (Olson *et al.* (1984).

Pathogenesis

Endometritis is a major postpartum disease which primarily affects dairy productivity and significantly increases economic losses in cattle (Turk *et al.*, 2011). Immediately after parturition, warm, fluid filled uterus with necrotic debris: facilitates multiplication of pathogenic microbes (Deori and Phookan, 2015). Moreover, earlier evidence suggests that pathogen may get excess to uterus through hematogenous route (Jeon *et al.*, 2017). Moreover, multiple bacterial infections are involved in endometritis. However, uterus attempts to get rid of these pathogens through infiltration of neutrophils, 21 days post-partum (Földi *et al.*, 2006; Sheldon *et al.*, 2006). In response, a huge number of inflammatory cells get involved against pathogens and that result in exudation and pus formation. Unfortunately, postpartum infection in the uterus with bacteria disrupt physiological events in dairy cattle, leading to the development of uterine diseases (Sheldon *et al.*, 2008; Turk *et al.*, 2011). Moreover, severity of infection depends on the bacterial load, pathogenicity and the immune status of cow (Sheldon *et al.*, 2002; LeBlanc *et al.*, 2011; Jeon *et al.*, 2016). Similarly, the most common intrauterine pathogens are *Escherichia coli, T. pyogenes*, *Fusobacterium necrophorum* and *Prevotalla spp*. (Földi *et al*., 2006; Sheldon *et al*., 2006). However, pathogenicity of uterine infection is still not clear; nonetheless, virulent factors of bacteria are responsible for uterine pathology. Additionally, presence of high pro-inflammatory cytokine concentration is obvious in immune response, and peripheral circulation indicate acute phase proteins with seldom signs of systemic disease (Sheldon *et al.*, 2006).

A positive correlation has been observed in between *Streptococcus uberis* and *T. pyogenes* infections 3rd day of postpartum. Similarily, *α-hemolytic Streptococci* increases the risk of purulent vaginal discharge (Werner *et al.*, 2012). The infected endometrium prohibits development and implantation of embryo. Furthermore, it decreases conception rates after resolution of disease (Sheldon, 2007). Likewise, endometrium cells in comparison to epithelial cells are more sensitive to *T. pyogenes*is pyolysin (a major virulent factor, PLO), mediated cytolysis.

After parturition*, T. pyogenes* emits harmful effects on endometrium and severely disrupts it (Amos *et al.*, 2014). In addition, uterine infection disrupts the endocrine function by releasing of PGF2 α? and also delays luteolysis. Moreover, the inflammation causes scaring and adhesion of endometrium, and oviduct and consequently leads to interruption in conception (Sheldon, 2007)**.**

In fact, genital tract has innate immunity and it highly depends on the pattern recognition receptors (PRRs), it detects the pathogen through pattern associated molecular patterns (PAMPs). PRRs belong to Toll-like Receptors (TLRs) family. These detect a variety of PAMPs related with fungi, bacteria and viruses. Similarly, epithelial and stromal cells express the toll like receptor 4 (TLR4), the receptor for lipo-polysaccharide (endotoxin, LPS), which is the key PAMP in uterus to detect pathogenic *E. coli* (Beutler, 2004; Herath *et al.*, 2006). Further, it interrupts in the restoration of immunological homeostasis and ovarian oestrus cycle obligatory for consecutive fertility. It also plays role in innate immunity, by release of cytokines and chemokines via binding of Toll-like receptors (TLR) with LPS. These chemokines stimulate neutrophils and macrophages to eliminate the bacteria from uterus (Sheldon *et al.*, 2009). Besides, understanding of pathogenesis and the various effects on reproductive hormones have been illustrated in Figure 2.

The severity and persistence of infection in the uterus depends on the degree of contamination, uterine defense mechanism and presence of substrates (such as devitalized tissues) for the microbial growth (Deori and Phookan, 2015). Delayed ovulation is a consequence of cytokine and toxins released by bacteria. This suppresses gonadotrophin releasing hormone (GnRH), and thus disrupts the secretion of luteinising hormone (LH) (Sheldon, 2007)**.** Moreover, conception rates and decreased fertility in animals due to adverse effect of inflammatory responses on brain, that controls the ovary functions including follicle growth. Uterine infection reduces the follicular growth and compromised function has been reported by observing reduced oestradiol secretion (Sheldon, 2007)**.**

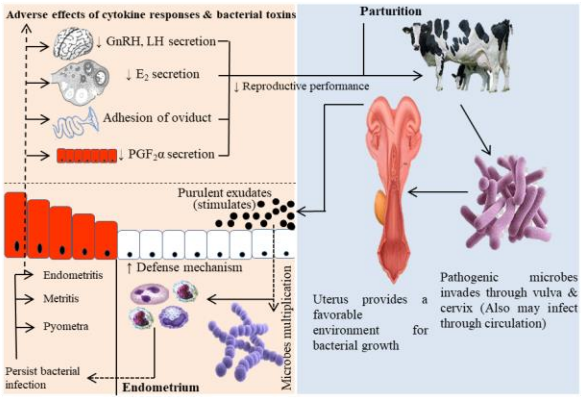

Figure 2. Pathogenesis of endometritis

Clinical signs

After 3 to 4 days of artificial insemination, pus flakes might be observed intra-vaginally and within vulvar lips. Similarly, vaginal mucopurulent discharge (whitish yellow in colour) can be observed in clinical endometritis whilst an affected cow lies down (Kumar, 2015). Doughy consistency of uterus around the ovaries and persistent corpus luteum can be palpated during rectal palpation (Kahn *et al.*, 2005; Abdullah *et al.*, 2015). Reduction in milk production and infertility signifies uterine infection in cows. Nevertheless, no any clinical sign of systemic illness is present, comparable to septic puerperal metritis (Kumar, 2015).

Diagnosis

In fact, infected animal demonstrate typical or prolonged oestrus cycle (Kumar, 2015). Similarly, uterine infection can be diagnosed though rectal palpation in bovine (LeBlanc *et al.*, 2002). Although, vaginal speculum or clean gloved hand can be used for reproductive tract inspection, whilst, uterine horns can be felt as distinctly thick and distended on palpation (Kumar, 2015). Discharged mucus is the best choice for the diagnosis of endometritis. Microscopically, increased number of WBCs along with epithelial cells can noticed in mucus smear. Moreover, diagnosis of metritis and clinical endometritis must include evaluation of

female genital tract contents collected by speculum or insertion of a clean gloved hand through vagina (Kumar, 2015).

Besides, manually collected pus and evaluation of its odour is major indicator for assessment and scoring the severity of disease that can augment treatment (LeBlanc *et al.*, 2002; Abdel-Latif *et al.*, 2016), mucus can also be used in white side test for diagnosis of endometritis (Kumar, 2015). After 20 days postpartum, a purulent uterine discharge can be observed while, in case of clinically defined relevant endometritis can be seen after 26 days of onset of endometritis (LeBlanc *et al.*, 2002; Gautam *et al.*, 2009). Moreover, intra-uterine fluid provides reliable results in the diagnosis though ultra-sonography after 3 weeks of postpartum (MSD, 2019).

Treatment

Treatment protocol must focus on causative bacteria and the restoration of reproductive performance. Some of the earlier studies have shown that the use of clinical and bacteriological remedy is the endpoint for endometritis treatment (Callahan and Horstman, 1993; Dohmen *et al.*, 1995; Brooks, 2000), rather than taking appropriate economic measures for pregnancy timing required for maintaining reproductive performance (LeBlanc *et al.*, 2002).

Ever since, due to significance of bacterial resistance (a public health concern globally since last two decades), treatment of endometritis has got much consideration (Gilbert and Schwark, 1992). Moreover, drug resistant bacterial strains are increasing and cause a serious problem during clinical treatments of human as well as animal infectious diseases. Thus, the prime objective of the treatment is to reduce the persistence of uterine infection, quick recovery and reestablishment of fertility. Basically, the objective is to reduce the load of pathogenic microorganisms and also stimulate local defence of uterus as repair occurs (LeBlanc *et al.*, 2002).

Similarly, a lot of treatment protocols have been devised, mainly focusing on the elimination of bacteria from the uterus, reduce the inflammation and restore the functions of endometrium. Additionally, antibiotics used as an intra-uterine infusion is the first line of treatment but requires a 24 hours withdrawal period of milk in Japan. Moreover, it is associated with the development of anti-microbial resistance (Heuwieser *et al.*, 2000). Conversely, PGF2α administration merely requires a milk withdrawal period as bacterial resistance has not yet been reported. Similarly, PGF2α is used efficiently as strategic treatment in endometritis during early postpartum period. Factually, it improves the reproductive performance, accelerates the process of luteolysis and uterine involution (Tenhagen and Heuwieser, 1999; Kasimanickam *et al.*, 2005).

Several studies have been carried to establish benefits of intrauterine antibiotics in endometritis (Steffan *et al.*, 1984; Thurmond *et al.*, 1993). Dubuc *et al.* (2011) reported that two different treatments of PGF2α administered at days 35 and 49 of postpartum for endometritis, diagnosed through cytological assessment did not improve the reproductive performance. While many comparative trials on clinical findings (Steffan *et al.*, 1984; Sheldon and Noakes, 1998) and reviews (Gilbert and Schwark, 1992; Olson, 1996) have reported that the PGF2*α* is at least and effective and referable for use as intrauterine infusion (i.u) for endometritis treatment. Likewise, therapeutic approaches could be followed in cause of endometritis on the basis of increased uterine contraction, stimulation of defence mechanism of uterus, to overcome infection and repair the damage of endometrium (Kumar, 2015). Further, antimicrobial therapy including penicillin is choice of drug and even effective in the presence of pus in the uterus. Similarly, oxytetracycline is the most effective treatment for mixed pathogenic population of micro-organisms in early post-partum phase (Kumar, 2015).

Control

Uterine infections and prevalence of endometritis can be minimized through good management during pre and postpartum period. Inappropriately, effective treatment options against the endometritis remains limited as the disease can persist after treatment and recovery. Consequently, it is highlighted that the treatment is not a solution for the endometritis disease, but, implementation of effective prevention as well as control measures must also be taken in consideration during the disease (Ganaie *et al.*, 2018).

Management interventions (MIs) to prevent the introductions and to reduce the spread of pathogens into the herd are the critical components of good management practices at herd level (Wolff *et al.*, 2019). It could significantly minimize the endometritis incidences, which will increase the productivity

and profitability of dairy herds. The situation can also be supported by extension and advisory support by relevant departments /government side in pre and postpartum periods augments the prevention and control of endometritis in dairy herds (Tayebwa *et al.*, 2015). Another technique, Best worst scaling (BWS) is a choice and preferred technique in modern countries to gather the different expert opinion on the effective biosecurity measures for dairy farms (Hansson and Lagerkvist, 2016; Shortall *et al.*, 2017). The BWS is frequently used in the different fields such as market research, human health, and agriculture and livestock management sciences.

In spite of cost effective, drawbacks of antibiotic administration have withdrawal effects. Antibiotics residues present in food, such as milk and meat and also developed antibiotic resistance causes disturbance in the normal defense mechanism of the uterus results in permanent infertility in animals ((Overton and Fetrow, 2008; Deori and Phookan, 2015). Therefore, a best tool to prevent bacterial disease is to follow vaccination programs in dairy farm to minimize the antibiotics uses (Talbot and Lacasse, 2005). Endometritis have multiple causative agents thus an efficient multivalent vaccine could play a major role in disease control. On the other hand, the hormonal as well as antibiotic therapies are not only expensive but out of reach of the farmer as well his affordability in Pakistan.

CONCLUSION

Endometritis is one of the significant and foremost prevalent diseases in cattle populations globally. In addition, responsible authorities i.e. government and NGOs must take this devastating condition seriously and start awareness campaign to create an understanding amongst local farmers of Pakistan. Moreover, awareness campaign must cover all aspects from nutrition to pregnancy, hygienically handling of dystocia, artificial insemination. Additionally, professionals and technical staff must be properly trained and equipped in all diagnosis techniques and proper treatment; which is a foremost hurdle due to multiple causative agents. More importantly a multivalent vaccine (an effective measure to control endometritis) should be made available commercially. Whereas, the wide use of antibiotics with reproductive hormonal treatment may not be suggested due to their residual drawback and is a public health hazard.

AUTHOR'S CONTRIBUTION

M. Umer: Study conception and design, draft writing
S. F. Syed: Manuscript writing and revision
Bunesh: Drafting the article
Q. A. Shah: Critical revision of the article
I. U. Kakar: Revision of the article and proof reading

REFERENCES

Abdel-Latif, M., E. S. EL-Gohary, A. Gabr, A. El-Hawary, S. Ahmed, S. Ebrahim and M. M. Fathala. 2016. Impact of supplementing propylene glycol and calcium propionate to primiparous buffalo cows during the late gestation and early lactation period on reproductive performance and metabolic parameters. Alexandria Journal for Veterinary Sciences, 51 (1): 114-121.

Abdullah, F., E. Chung, Y. Abba, A. Tijjani, M. Sadiq, K. Mohammed, A. Osman, L. Adamu, M. Lila and A. Haron. 2015. Management of clinical case of endometritis in a cow: A case report. Journal of Veterinary Advances, 5 (4): 887-890.

Amos, M. R., G. D. Healey, R. J. Goldstone, S. M. Mahan, A. Düvel, H.-J. Schuberth, O. Sandra, P. Zieger, I. Dieuzy-Labaye and D. G. Smith. 2014. Differential endometrial cell sensitivity to a cholesterol-dependent cytolysin links Trueperella pyogenes to uterine disease in cattle. Biology of Reproduction, 90 (3): 54, 1-13.

Azawi, O. and Z. J. Azar. 2002. Bacteriological and histopathological studies in repeat breeder cows. Iraqi Journal of Veterinary Science, 16: 49-59.

Azawi, O., S. Omran and J. Hadad. 2008a. A study of endometritis causing repeat breeding of cycling Iraqi buffalo cows. Reproduction in Domestic Animals, 43 (6): 735-743.

Azawi, O., M. Rahawy and J. Hadad. 2008b. Bacterial isolates associated with dystocia and retained placenta in Iraqi buffaloes. Reproduction in Domestic Animals, 43 (3): 286-292.

Beutler, B. 2004. Innate immunity: An overview. Molecular Immunology, 40 (12): 845-859.

Brooks, G. 2000. Comparison of two intrauterine treatments for bovine endometritis. Veterinary Record, 146 (1).

Callahan, C. and L. Horstman. 1993. Treatment of postpartum metritis in dairy cows caused by Actinomyces pyogenes. The Bovine Practitioner, 162-165.

Cheong, S., D. Nydam, K. Galvão, B. Crosier and R. Gilbert. 2011. Cow-level and herd-level risk factors for subclinical endometritis in lactating Holstein cows. Journal of Dairy Science, 94 (2): 762-770.

Deori, S. and A. Phookan. 2015. Bovine postpartum metritis and its therapeutics: A Review. Indian Journal of Science and Technology, 8 (23): 1.

Dohmen, M., J. Lohuis, G. Huszenicza, P. Nagy and M. Gacs. 1995. The relationship between bacteriological and clinical findings in cows with subacute/chronic endometritis. Theriogenology, 43 (8): 1379-1388.

Dubuc, J., T. Duffield, K. Leslie, J. Walton and S. LeBlanc. 2010. Definitions and diagnosis of postpartum endometritis in dairy cows. Journal of Dairy Science, 93 (11): 5225-5233.

Dubuc, J., T. Duffield, K. Leslie, J. Walton and S. LeBlanc. 2011. Randomized clinical trial of antibiotic and prostaglandin treatments for uterine health and reproductive performance in dairy cows. Journal of Dairy Science, 94 (3): 1325-1338.

Földi, J., M. Kulcsar, A. Pecsi, B. Huyghe, C. De Sa, J. Lohuis, P. Cox and G. Huszenicza. 2006. Bacterial complications of postpartum uterine involution in cattle. Animal Reproduction Science, 96 (3-4): 265-281.

Galvão, K., L. Greco, J. Vilela, M. Sá Filho and J. Santos. 2009. Effect of intrauterine infusion of ceftiofur on uterine health and fertility in dairy cows. Journal of Dairy Science, 92 (4): 1532-1542.

Ganaie, B. A., F. Sultan, R. R. Dar and F. Ahmad. 2018. Uterine infection in dairy animals and its ameliorative measures: a review. Journal Pharmacognosy and Phytochemistry, 7 (1): 194-199.

Gautam, G., T. Nakao, M. Yusuf and K. Koike. 2009. Prevalence of endometritis during the postpartum period and its impact on subsequent reproductive performance in two Japanese dairy herds. Animal Reproduction Science, 116 (3-4): 175-187.

Gilbert, R. O. and W. S. Schwark. 1992. Pharmacologic considerations in the management of peripartum conditions in the cow. Veterinary Clinics of North America: Food Animal Practice, 8 (1): 29-56.

Griffin, J. F. T., P. J. Hartigan and W. R. Nunn. 1974. Non-specific uterine infection and bovine fertility. I. Infection patterns and endometritis during the first seven weeks post-partum. Theriogenology, 1: 91-96.

Hansson, H. and C. Lagerkvist. 2016. Dairy farmers' use and non-use values in animal welfare: Determining the empirical content and structure with anchored best-worst scaling. Journal of Dairy Science, 99 (1): 579-592.

Herath, S., D. Fischer, P, D. Werling, E. Williams, J, S. Lilly, T, H. Dobson, C. Bryant, E and I. M. Sheldon. 2006. Expression and function of Toll-like receptor 4 in the endometrial cells of the uterus. Endocrinology, 147 (1): 562-570.

Heuwieser, W., B. A. Tenhagen, M. Tischer, J. Lühr and H. Blum. 2000. Effect of three programmes for the treatment of endometritis on the reproductive performance of a dairy herd. Veterinary Record, 146 (12): 338-341.

Hussain, A., R. Daniel and D. O'Boyle. 1990. Postpartum uterine flora following normal and abnormal puerperium in cows. Theriogenology, 34 (2): 291-302.

Jeon, S. J., F. Cunha, X. Ma, N. Martinez, A. Vieira-Neto, R. Daetz, R. C. Bicalho, S. Lima, J. E. Santos and K. C. Jeong. 2016. Uterine microbiota and immune parameters associated with fever in dairy cows with metritis. PloS one, 11 (11): e0165740.

Jeon, S. J., F. Cunha, A. Vieira-Neto, R. C. Bicalho, S. Lima, M. L. Bicalho and K. N. Galvão. 2017. Blood as a route of transmission of uterine pathogens from the gut to the uterus in cows. Microbiome, 5 (1): 1-13.

Kahn, C., L. Scott and S. Aiello. 2005. The Merck veterinary manual 9th Ed. Copyright (C) by Merck Co., Inc printed in the USA by National Publishing. Inc. Philadelphia, Pensylvania, 146-148.

Kasimanickam, R., T. Duffield, R. Foster, C. Gartley, K. Leslie, J. Walton and W. Johnson. 2005. The effect of a single administration of cephapirin or cloprostenol on the reproductive performance of dairy cows with subclinical endometritis. Theriogenology, 63 (3): 818-830.

Khan, H. H., Z. I. Qureshi, M. S. Waqas, M. H. Rashid, M. S. Saeed, S. Ali and M. Hassan. 2020. Prevalence and drug susceptibility of mycotic endometritis in Sahiwal cattle in district Faisalabad, Pakistan. Pakistan Veterinary Journal, 40 (4): 461-466.

Khan, M. S., Z. Rehman, M. A. Khan and S. Ahmad. 2008. Genetic resources and diversity in Pakistani cattle. Pakistan Veterinary Journal, 28 (2): 95-102.

Kumar, P. 2015. Applied Veterinary Gynaecology and Obstetrics. CBS Publishers and Distributors Pvt. Ltd. New Delhi-110002. pp. 258-271.

LeBlanc, S., T. Duffield, K. Leslie, K. Bateman, G. P. Keefe, J. Walton and W. Johnson. 2002. Defining and diagnosing postpartum clinical endometritis and its impact on reproductive performance in dairy cows. Journal of Dairy Science, 85 (9): 2223-2236.

LeBlanc, S. J., T. Osawa and J. Dubuc. 2011. Reproductive tract defense and disease in postpartum dairy cows. Theriogenology, 76 (9): 1610-1618.

Martinez, J. and M. Thibier. 1984. Reproductive disorders in dairy cattle: I. Respective influence of herds, seasons, milk yield and parity. Theriogenology, 21 (4): 569-581.

MSD, 2019. Manual Veterinary Manual. Utrine diseases in dairy cattle. Web site. https://www.msdvetmanual.com/reproductiv e-system/ metritis- in-large-animals/acute-puerperal-metritis-in-large-animals.

Noakes, D., D. Till and G. Smith. 1989. Bovine uterine flora post partum: a comparison of swabbing and biopsy. The Veterinary Record, 124 (21): 563-564.

Noakes, D., L. Wallace and G. Smith. 1990. Pyometra in a Friesian heifer: bacteriological and endometrial changes. Veterinary Record, 126 (20): 509.

Olson, J., L. Ball, R. Mortimer, P. Farin, W. Adney and E. Huffman. 1984. Aspects of bacteriology and endocrinology of cows with pyometra and retained fetal membranes. American Journal of Veterinary Research, 45 (11): 2251-2255.

Olson, J. D. 1996. Metritis/Endometritis. Paper presented at the American Association of Bovine Practitioners Proceedings of the Annual Conference.

Overton, M. and J. Fetrow. 2008. Economics of postpartum uterine health. Proceeding Dairy Cattle Reproduction Council, pp. 39-44.

Potter, T. J., J. Guitian, J. Fishwick, P. J. Gordon and I. M. Sheldon. 2010. Risk factors for clinical endometritis in postpartum dairy cattle. Theriogenology, 74 (1): 127-134.

Ruder, C., R. Sasser, R. Williams, J. Ely, R. Bull and J. Butler. 1981. Uterine infections [*Corynebacterium pyogenes* and *Fusobacterium necrophorum*] in the postpartum cow: I. Effect of dietary crude protein restriction. Theriogenology.

Sheldon, I. 2007. Endometritis in cattle: pathogenesis, consequences for fertility, diagnosis and therapeutic recommendations. Partners in Reproduction, 2 (1): 1-5.

Sheldon, I. and D. Noakes. 1998. Comparison of three treatments for bovine endometritis. Veterinary Record, 142 (21): 575-579.

Sheldon, I., D. Noakes, A. Rycroft, D. Pfeiffer and H. Dobson. 2002. Influence of uterine bacterial contamination after parturition on ovarian dominant follicle selection and follicle growth and function in cattle. Reproduction, 123 (6): 837-845.

Sheldon, I. M., J. Cronin, L. Goetze, G. Donofrio and H. J. Schuberth. 2009. Defining postpartum uterine disease and the mechanisms of infection and immunity in the female reproductive tract in cattle. Biology Reproduction, 81 (6): 1025-1032.

Sheldon, I. M. and H. Dobson. 2004. Postpartum uterine health in cattle. Animal Reprod Science, 82-83: 295-306.

Sheldon, I. M., G. S. Lewis, S. LeBlanc and R. O. Gilbert. 2006. Defining postpartum uterine disease in cattle. Theriogenology, 65 (8): 1516-1530.

Sheldon, I. M., E. J. Williams, A. N. Miller, D. M. Nash and S. Herath. 2008. Uterine diseases in cattle after parturition. The Veterinary Journal, 176 (1): 115-121.

Shortall, O., M. Green, M. Brennan, W. Wapenaar and J. Kaler. 2017. Exploring expert opinion on the practicality and effectiveness of biosecurity measures on dairy farms in the United Kingdom using choice modeling. Journal of Dairy Science, 100 (3): 2225-2239.

Sohail, M., H. Uddin and M. Nauman-ul-Islam. 2018. Prevalence and therapeuti c measures of postpartum uterine diseases in achai cattle at livestock research and development station Surezai, Peshawar. Journal of Dairy and Veterinary Animal Reserach, 7 (4): 150-152.

Steffan, J., S. Adriamanga and M. Thibier. 1984. Treatment of metritis with antibiotics or prostaglandin F_2 alpha and influence of ovarian cyclicity in dairy cows. American Journal of Veterinary Research, 45 (6): 1090-1094.

Talbot, B. G. and P. Lacasse. 2005. Progress in the development of mastitis vaccines. Livestock Production Science, 98 (1-2): 101-113.

Tayebwa, D. S., G. Bigirwa, J. Byaruhanga and K. I. Kasozi. 2015. Prevalence of endometritis and its associated risk factors in dairy cattle of Central Uganda. Journal of

Experimental Agriculture International, pp. 155-162.

Tenhagen, B. and W. Heuwieser. 1999. Comparison of a Conventional Reproductive Management Programme Based on Rectal Palpation and Uterine Treatment of Endometritis with a Strategic Prostaglandin F2α. Programme. Journal of Veterinary Medicine; Series A, 46 (3): 167-176.

Thurmond, M., C. Jameson and J. Picanso. 1993. Effect of intrauterine antimicrobial treatment in reducing calving-to-conception interval in cows with endometritis. Journal of the American Veterinary Medical Association, 203 (11): 1576-1578.

Turk, R., M. Samardžija and G. Bačić. 2011. Oxidative stress and reproductive disorders in dairy cows. Marek, ER, Dairy cows: Nutrition, fertility and milk production. Nova Science Publishers, New York, USA, pp. 57-98.

Werner, A., V. Suthar, J. Plöntzke and W. Heuwieser. 2012. Relationship between bacteriological findings in the second and fourth weeks postpartum and uterine infection in dairy cows considering bacteriological results. Journal of Dairy Science, 95 (12): 7105-7114.

Wolff, C., S. Abigaba and S. S. Lewerin. 2019. Ugandan cattle farmers' perceived needs of disease prevention and strategies to improve biosecurity. BMC Veterinary Research, 15 (1): 1-11.

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