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.
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 postpartum (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 Prevotella 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. Similarly, 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* pyolyisin (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 PGF2α 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](image)

**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 antimicrobial 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 PGF2α 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 (Mls) 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
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Bunesh: Drafting the article
Q. A. Shah: Critical revision of the article
I. U. Kakar: Revision of the article and proof reading

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