



Postpartum endometritis in dairy cows: current status of diagnosis, therapy and prevention

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Abstract

Clinical (CE) and subclinical endometritis (SCE) occur a few or several weeks postpartum in dairy cows. Immunosuppression, microbial proliferation and disruption of endometrial lining of the uterus are risk for the development of metritis which can be associated with increased likelihood of development of endometritis. Diagnostic approaches for CE have utilized the vaginoscopic presence of pus in the vaginal lumen as the common diagnostic criterion although currently Metrichick and ultrasonography are preferred procedures. The identification of pathologic numbers of microbes in the uterus appears difficult unless the samples are collected using specialized instruments. Inflammatory changes in the endometrium (of CE affected cows) can be identified with high accuracy in histologic sections of the endometrial biopsy specimens or hysteroscopy however, such approaches are limited to specialized cases only. Cows with SCE evidence a cervico-vaginal discharge without pathogenomic properties (pus and or altered consistency) and thus the diagnosis of SCE continues to be presumptive in cows with lowered fertility. Ultrasonography and uterine cytology on swabs or fluids collected from uterus have been considered accurate for the diagnosis of SCE. The diagnostic criterion in uterine cytology is the presence of higher (5-18%) polymorphonuclear leucocytes (PMNs) during 22-45 days postpartum. However

there is lack of consensus in the cutoff percent of PMNs for establishing SCE in cows at different days postpartum. Therapeutic approaches for CE have suggested the systemic and intrauterine infusion of antimicrobials, IM administration of prostaglandins and chemotractant agents or antioxidants infused intrauterine. There is a lack of consensus in many studies on the usefulness of intrauterine infusion of antimicrobials and systemic prostaglandins especially in terms of overall improvement of subsequent fertility. The intrauterine infusion of chemotractant agents and antioxidants offer potential benefit over other therapies particularly for SCE. Preventive measures for endometritis include the administration of selenium and vitamin E, however peri-parturient management of cows appears to be of utmost significance. It was concluded that diagnostic approaches for CE and SCE need validation and till then presence of pus in vaginal secretions is the easiest approach for diagnosis. Therapy of CE and SCE should be weighed against the potential benefits and residue implications and the severity of the condition. Periparturient management of dairy cows appears to be the most appropriate preventive measure.

Keywords: Clinical endometritis, subclinical endometritis, uterine cytology, antimicrobials, prostaglandin.

Postpartum endometritis of dairy cows continues to be a major cause of poor fertility and delayed conceptions (Couto *et al.*, 2013). The postpartum uterine defense mechanisms strive to maintain equilibrium for uterine health by reducing the number of pathogenic bacteria; and when these mechanisms are disrupted the endometrial lining of the uterus is affected with resultant growth of microbes and poor fertility. Although many predisposing factors such as parity (Aghamiri *et al.*, 2014), rearing systems (Chunjie *et al.*, 2013), postpartum complications (Islam *et al.*, 2014), negative energy balance during the postpartum period (Yasui *et al.*, 2014), high prepartum plasma non esterified fatty acids and high postpartum beta hydroxybutyrates (Giuliodori *et al.*, 2013), have been mentioned, the most plausible explanation for postpartum uterine infections appears to be the immune suppression in parturient cows (Guo Qing *et al.*, 2011; Kimura *et al.*, 2014) probably with resultant decreased interleukins (Islam *et al.*, 2013), low levels of proinflammatory cytokines (Galvao, 2011) and increased concentrations of nitric oxide (Li De Jun *et al.*, 2010) and free oxygen radicals.

Two important types of endometritis have been recently recognized; the clinical (CE) and subclinical endometritis (SCE) with difficulty in diagnosing the latter (Foldi *et al.*, 2006; Barlund *et al.*, 2008). The diagnosis of clinical (CE) endometritis has been based on manual examination, vaginoscopy Metricheck or ultrasonography. Under most clinical settings presence of pus in the vaginal discharges or estrus mucus is considered sufficient evidence that the cow harbors infection in the

uterus. The diagnosis of SCE is based on uterine cytology (Kasaimanickam *et al.*, 2004; Gilbert *et al.*, 2005; Kumar *et al.*, 2013) and ultrasonography. Most approaches utilizing uterine cytology for the diagnosis of SCE differ in the cut off percent of polymorphonuclear leucocytes (PMNs) for establishing endometritis in cows at different days postpartum (Dubuc *et al.*, 2010; Couto *et al.*, 2013; Madoz *et al.*, 2013; Brodzki *et al.*, 2014). The therapies mentioned for endometritis have been equivocal. Studies differ in the efficacy and usefulness of infusing antibiotics in the uterus (Knutti *et al.*, 2000; Refsdal, 2000; McDougall, 2001) or the administration of hormones such as prostaglandins (Laven, 2003) which favor uterine clearance of pathogenic material. A wide variety of chemottractant agents such as hyperimmune serum (Ahmadi *et al.*, 2014), autologous plasma (Sarma *et al.*, 2010), *E. coli* lipopolysaccharides and oyster glycogen (Sarma *et al.*, 2010) or antioxidants (Kaveh *et al.*, 2014) have been suggested as alternative therapy to infusion of antibiotics. In this review we mention the efficiency of diagnostic approaches and therapies commonly used for endometritis in dairy cows.

Diagnostic approaches

Clinical records of periparturient problems helps in identifying the animals at risk of uterine disease but does not provide specific diagnosis (Markusfeld, 1987; McDougall, 2001). Clinical endometritis is diagnosed by the presence of purulent uterine discharge or cervical diameter >7.5cm, or mucopurulent discharge after 26 days in milking (LeBlanc, 2008).

The simplest approach for diagnosis of clinical endometritis is manual examination of vagina and withdrawal of the mucus for inspection (Sheldon *et al.*, 2002). Such technique is considered inexpensive, quick and provides additional sensory information such as detection of vaginal lacerations and detection of odor of mucus in vagina. Visual inspection of the vaginal canal using a sterile metal or transparent barrel with a light source (Vaginoscopy) has been used to inspect the presence of pus or abnormal discharge not extruding out of the vulvar lips (Runciman *et al.*, 2008a; Leutert *et al.*, 2012). Vaginoscopy has been considered more sensitive than simple external inspection for detection of purulent discharge (Dohmen *et al.*, 1995; Le Blanc *et al.*, 2002a). Vaginoscopy correctly predicted the uterine infection in 59-82% of cases (Miller *et al.*, 1980; Dohmen *et al.*, 1995; Williams *et al.*, 2005; Leutert *et al.*, 2012) but vaginitis, cervicitis, cystitis and purulent nephritis may give false results. Vaginoscopy is convenient to use yet there is risk of disease transmission (LeBlanc *et al.*, 2002a). During recent years a device "Metricheck" was developed, that is used to retrieve vaginal contents. Vaginal mucus is assessed for color, proportion and volume of pus and odor

resulting in endometritis clinical score; it is prognostic for the likely outcome of treatment (Sheldon and Noakes, 1998). This approach is considered useful for the veterinarian to evaluate the presence and growth density of pathogenic bacteria contaminating postpartum uterine lumen (Williams and Sheldon, 2003; McDougall *et al.*, 2007; Pleticha *et al.*, 2009; Peter *et al.*, 2011). The vaginal mucus is characterized using an endometritis scoring system (Williams *et al.*, 2005).

In one study (Williams *et al.*, 2005) mucopurulent discharge was associated with *Fusobacterium necrophorum* and purulent discharge was associated with *Arcanobacterium pyogenes* and *Proteus sp.*, whilst a fetid odor was associated with a greater load of *Arcanobacterium pyogenes*, *E.coli*, *Streptococci*, *Mannheimia haemolytica*.

For clinical endometritis transrectal palpation is most common means of diagnosis but palpation correctly identified only 22% of cows predicted to have uterine infection, compared to uterine culture (Miller *et al.*, 1980). For definitive diagnosis of clinical endometritis microbiological examination of swabs collected from uterine lumen has been suggested, yet the difficulty in obtaining samples representative of the uterus limit the frequent use of such approach (Purohit, 2008). Swab is most accurate means of obtaining samples for identification of bacteria that cause infection (Olson *et al.*, 1986; Noakes *et al.*, 1991; Bonnett *et al.*, 1993). Bacterial culture determine the microbes (Studer and Morrow, 1978; Olson *et al.*, 1986; Bretzlaff, 1987; Lewis, 1997; Bondurant, 1999; LeBlanc *et al.*, 2002b; Sheldon *et al.*, 2004) in the uterus causing the pathology. For swabs collected from uterine lumen of dairy cows 21 and 28 days after calving, purulent vaginal mucus was associated with growth density of pathogenic bacteria but not opportunist contaminants which includes *Arcanobacterium pyogenes*, *Fusobacterium necrophorum*, *Prevotella sp.*, *Bacteroides* (Dohmen *et al.*, 1995; Williams *et al.*, 2005; Westermann *et al.*, 2010). The coagulation of cervico-vaginal mucus on boiling with NaOH (and resultant yellow color in endometritis) had been suggested to test the presence of inflammatory exudates (White side test), however due to inconsistent results such test have not been validated (Purohit, 2008) or suggested (Raja *et al.*, 2012).

The definitive diagnosis of clinical endometritis has been suggested by a few to be based upon histological examination of endometrial biopsies (Bonnett *et al.*, 1993; Meira Junior, 2010; Dolatkah *et al.*, 2013). An endometrial tissue is obtained with a biopsy punch. Ideal sample size is 10-20mm × 3mm, both epithelial cell layer and granular architecture (De Bois and Manspeaker, 1986). Histologically endometritis is characterized by disruption of endometrial epithelium, infiltration

of inflammatory cells and accumulation of lymphocytes, vascular congestion and stromal edema (Bonnett *et al.*, 1991; Bondurant, 1999; Meira Junior *et al.*, 2012). Endometrial inflammation is evidenced by increased number of inflammatory cells in foci or diffused in various areas of lamina propria. Acute inflammation contains more polymorphonuclear neutrophils (Bonnett *et al.*, 1991). Most commonly seen in chronic endometritis is infiltration of lymphocytes, accompanied by various degrees of plasma cell and macrophage infiltration (Kubar and Jalakas, 2002). However uterine biopsy followed by histologic examination is costly, time consuming, and not clinically accessible under most situations. Moreover biopsy has been associated with a detrimental effect on subsequent fertility (Miller *et al.*, 1980; Bonnett *et al.*, 1993). A non-invasive approach for the diagnosis of clinical endometritis in cows could be hysteroscopy (Madoz *et al.*, 2010) however due to the high cost of the equipment and the problems encountered in passing the bovine cervix the prospects of such a technique are currently limited and suggested for specialized cases only (Milosh *et al.*, 2013).

Subclinical endometritis is characterized by scanty exudates accumulated in uterus, resulting in complete lack of cervical discharge with pathogenomic property (Kasimanickam *et al.*, 2004; Gilbert *et al.*, 2005; Sheldon *et al.*, 2006). Diagnosis of SCE has been presumptive in the past and repeat breeder cows were considered to have SCE and transrectal palpation revealed no abnormality (Purohit, 2008). More recently transrectal ultrasonography and endometrial cytology has been suggested for the definitive diagnosis of SCE (Lenz *et al.*, 2007; Oral *et al.*, 2009; Melcher *et al.*, 2014). Ultrasonographic features helpful in diagnosis of SCE include accumulation of fluid and increased endometrial thickness (Lenz *et al.*, 2007; Oral *et al.*, 2009; Purohit *et al.*, 2013). Samples for cytology are collected using uterine biopsy, uterine lavage or cytobrush technique modified for large animals (Kasimanickam *et al.*, 2005). The collected swabs are rolled on glass microscopic slides fixed and stained with modified Wright Giemsa staining. Prepared smear must contain epithelial cells (to confirm correct site of collection), if no epithelial cells are seen, there is no assurance that the sample was taken from the uterus (Azawi, 2008). A positive endometrial cytology with >18% PMN leukocytes at 20-33 days in milking or positive endometrial cytology with >10% PMN leukocytes at 34-47 days in milking are considered diagnostic (Kasaimanickam *et al.*, 2004). Gilbert *et al.* (2005) used another technique, the low volume uterine flush to collect samples for endometrial cytology from cows between 40 and 60 days in milking. Samples in this approach was only 2-5 ml fluid yet, before staining it was suggested to be re-suspended and centrifuged by cytospin centrifuge (Foldi *et al.*, 2006). The cut off proportion of PMN leukocytes

diagnostic for subclinical endometritis was only 5% (Gilbert *et al.*, 2005; Foldi *et al.*, 2006). Thus approaches for uterine cytology differ in the technique and cutoff points of PMNs at different days postpartum. A recent study thus mentioned uterine cytology to diagnose subclinical endometritis is not practical under most clinical settings (Madoz *et al.*, 2014). Ultrasound examination may be used to identify some, but not all cases of subclinical endometritis (Kasimanickam *et al.*, 2004). Recent evaluations of the various diagnostic tests for the diagnosis of endometritis in dairy cows stated that there is a lack of validated, consistent definitions and outcome variables making comparisons of the different tests difficult (Boer *et al.*, 2014; Melcher *et al.*, 2014). Moreover the reproducibility of the various tests for SCE is low (Melcher *et al.*, 2014).

Therapy

The principle of treatment for endometritis is to reduce the load of pathogenic bacteria, enhance uterine defense and repair mechanism, thereby halt and reverse inflammatory changes that impair fertility (Le Blanc, 2008). Therapies advocated for endometritis include antibiotics, hormones and immunomodulators.

Antimicrobials

For treating endometritis antimicrobials are infused into the uterus and such therapies are aimed at achieving high concentrations of antibiotics at the site of infection (Gustafsson, 1984; Gilbert and Schwark, 1992). In contrast to systemic administration, intrauterine administration achieves higher drug concentration in endometrium, but there is little penetration to deeper layers of uterus or other genital tissues (Masera *et al.*, 1980; Bretzlaff *et al.*, 1983). There are a very few studies on the pharmacokinetics of drugs infused intrauterine and most evidence of improvement are based on clinical experiences. Substances used for intrauterine infusion for therapies of uterine infection include Tetracycline (Thurmond *et al.*, 1993; Sheldon and Noakes, 1998; Shams-Esfanabadi *et al.*, 2004), Penicillin (Thurmond *et al.*, 1993), Chloramphenicol (Steffan *et al.*, 1984), diluted Lugol's iodine (Callahan and Horstman, 1987), Gentamycin, Spectinomycin, Sulphonamides, Nitrofurazone, Iodine and Chlorhexidine (Gustafsson, 1984; Gilbert and Schwark, 1992), Florfenicol (Li Yan and Ji Lian, 2008), Ciprofloxacin (Purohit *et al.*, 2003; Singh *et al.*, 2004; Sunilchandra and Hiremath, 2004; Purohit and Sharma, 2007), Moxifloxacin (Purohit *et al.*, 2013), ceftriaxone (Mahto *et al.*, 2012), Cefquinome (Amiridis *et al.*, 2003) and Cephapirin (Dohmen *et al.*, 1995; McDoughall, 2001; Le Blanc *et al.*, 2002c; Runciman *et al.*, 2008b; Runciman *et al.*, 2009; Galvao *et al.*, 2009; Mosafieri *et al.*, 2013; Kumar *et al.*,

2013; Zobel, 2013). Treatment of genital infections in combination of 2 or 3 antibiotics preferably Gentamycin, Chloramphenicol and Enrofloxacin has also been suggested (Sood *et al.*, 2002). Intrauterine infusion of several antibiotics results in drug residues in milk (Kaneene *et al.*, 1986; Dinsmore *et al.*, 1996) and thus not permitted in many countries. Lugol's iodine and oxytetracycline are irritating and are reported to cause coagulation necrosis of endometrium (Gilbert and Schwark, 1992). In field trials, intra uterine infusion of antibiotics in a variety of protocols to treat endometritis has generally failed to show any benefit in reproductive performance over PGF2 (Steffan *et al.*, 1984; Thurmond *et al.*, 1993; Le Blanc, 2008). Thus, the intrauterine infusion of antibiotics continues to be controversial, however the authors feel that they should be used for clinical endometritis depending on the severity of infections. Oxytetracycline intrauterine administration represents a useful therapy, especially in treatment and prophylaxis of postpartum endometritis in cows (Chaudhery *et al.*, 1987; Khan and Khan, 1989; Singh *et al.*, 2001; Malinowski *et al.*, 2004). The direct intrauterine administration of oxytetracycline produces immediate therapeutic concentrations in caruncles and endometrium of both healthy and affected animals (Roncada *et al.*, 2000; Bateman *et al.*, 2002; Shams-Esfandabadi *et al.*, 2004; Kaczmarowski *et al.*, 2004) and because of its relatively lower absorption into blood stream (Roncada *et al.*, 2000), the therapeutic action is largely confined to uterine lumen and endometrium. Tetracycline's are known to be active under anaerobic conditions and are partly inactivated by purulent material, cell debris found in affected uterus (Cairolì *et al.*, 1993). Although intrauterine therapy is preferred treatment for endometritis, yet there are indications for use of systemic route of administration. Higher antibiotic concentrations throughout genital tract are achieved with systemic administration than with intrauterine therapy (Ott *et al.*, 1986; Bretzlaff, 1987). Systemic treatment is best if antibiotics are subjected to degradation by conditions in uterine lumen. A single subcutaneous administration of ceftiofur (1mg/kg) 24 h after calving resulted in peak concentrations of 2.85 ± 1.11 µg/mL at 2 h of administration and the concentration of ceftiofur in uterine tissues exceeded the minimal inhibitory concentration for common uterine pathogens (Okker *et al.*, 2002). Consecutive administration of ceftiofur (1mg/kg IM) for 3 days to cows with clinical endometritis at 21-27 days in milk resulted in clear vaginal discharge at 41-42 days in milk (Kaufmann *et al.*, 2010; Bartolome *et al.*, 2014). A single IM administration of oxytetracycline has been suggested to improve fertility in cows with subclinical endometritis (Tek *et al.*, 2010).

Hormones

In cows with functional corpus luteum, administration of exogenous PGF₂ is used to stimulate luteolysis, which reduce the progesterone and increase the estrogen concentrations, induce estrus and resolve uterine infections (Murray *et al.*, 1990; Lewis, 1997; Tenhagen and Heuwieser, 1999; Heuwieser *et al.*, 2000; Laven, 2003). Exogenous PGF₂ may enhance immune functions or increase uterine motility to help the uterus to resolve infections in animals that don't have active corpus lutea (Nakao *et al.*, 1997; Hirsbrunner *et al.*, 2003; Fernandes *et al.*, 2014). However the results of therapy of endometritis with prostaglandins in the absence of an active corpus luteum are inconsistent (Steffan *et al.*, 1984; Le Blanc *et al.*, 2002b). It has been recorded that PGF₂ has the least harmful effects and milk doesn't have to be discarded (Murray *et al.*, 1990; Mansour *et al.*, 2003). Successful treatment is evident by the clear vaginal discharge at subsequent estrus. Some reports indicate that PGF₂ is more effective when progesterone levels are high or corpus luteum is palpable (Sheldon and Noakes, 1998; Le Blanc *et al.*, 2002b). PGF₂ was equal to (Sheldon and Noakes, 1998) or tended to be more effective (Steffan *et al.*, 1984) than intrauterine penicillin or tetracycline for improvement of reproductive performance in cows with endometritis (Dubuc *et al.*, 2011). Numerous reviewers have concluded that PGF₂ appears to be at least as effective for endometritis as any available alternative therapy and presents minimal risk of harm to uterus or presence of residues in milk or meat (Paisley *et al.*, 1986; Gilbert and Schwark, 1992; Olsen, 1996). A 4 year study on Argentinian dairy cows employing prostaglandin treatment of endometritis affected cows revealed no improvement in the conception rates of primiparous cows (Mejia and Mengido, 2005) and similar views were expressed in another study (Hendricks *et al.*, 2006). A recent study (Lima *et al.*, 2013) stated that one or two treatments with PG to cows at 25 and 39 days in milk were unable to improve uterine health of postpartum cows.

Estradiol has been recommended by some to stimulate myometrium contractions, phagocytosis and mucus production (Roberts, 1986; Bretzlaff, 1987; Hussain, 1989). Estradiol at doses of 5-10 mg per animal has been used therapeutically for postpartum endometritis and is as effective as PGF₂ (Pepper and Dobson, 1987; Sheldon and Noakes, 1998). However the interval from treatment to conception was longer with estradiol treatment than PGF₂ or intrauterine antibiotic (Sheldon and Noakes, 1998). The use of estradiol has been banned in some countries owing to certain higher residues (Bretzlaff, 1987). Moreover administration of estradiol to lactating cows can suppress milk production and can result into formation of ovarian cysts (Roberts, 1986; Gumen *et al.*, 2002; Jeengar *et al.*, 2014) and thus

the use of estrogens is not advocated on a wider scale and should be limited to a short term therapy only under specific circumstances.

Immunomodulators and antioxidants

Approaches utilizing stimulation of the uterine defense mechanism to combat infection have mentioned the single intrauterine infusion of E Coli lipopolysaccharides (LPS) (100µg in 60 mL PBS), oyster glycogen (500 mg in 60 mL PBS) and autologous plasma (Singh *et al.*, 2000; Dhaliwal *et al.*, 2001; Methai *et al.*, 2005; Sahadev *et al.*, 2007; Sarma *et al.*, 2010) or hyper immune serum (Ahmadi *et al.*, 2014). These infusions act as potent chemottractant with resultant increased influx of polymorphonuclear leucocytes within the uterine lumen and significant decrease in uterine infection. However their routine use has not become popular due to high costs and poor availability.

The reactive oxygen species such as nitric oxide are known to be increased in the uterus of endometritis affected cows (Li De Jun *et al.*, 2010). The decreased clearance of free oxygen radicals in the uterine lumen have been attempted to be resolved by the intrauterine infusion of 50 mL super oxidized water (Kaveh *et al.*, 2014), 50-100 mL of 3% hydrogen peroxide (Dolezel *et al.*, 2010), infusion of ozone (Zobel, 2013; Duricic *et al.*, 2014), formosulfathiazole (Mari *et al.*, 2012), enzymes such as EDTA + Tris or lysosome (Ravikumar *et al.*, 2006), lysobutilin (Biziulevichius *et al.*, 1998), vitamin A, E and selenium (Sengupta and Nandi, 2013) and intrauterine infusion of vitamin C (Purohit, 2008). A commonly used intrauterine preparation in many countries contains metacresol sulfonic acid and formaldehyde (414 mg/mL) (Lotagen, Schering Plough, USA) and has been suggested to be infused intrauterine with distilled water once or more times during puerperium (Cutuk *et al.*, 2012) or in cows with endometritis not responding to routine therapy (Tenhagen and Heuwieser, 1999) with appreciable benefits. Despite the potential for improving fertility through antioxidant administration, results have been inconsistent. In a study in Mexico IM injection of vitamin E and selenium at Day 30 after calving did not affect first service conception rate but tended to increase conception rate at second service (Arechiga *et al.*, 1998). Similarly there was no benefit of multiple injections of β-carotene on fertility of lactating cows (Gossen *et al.*, 2004).

Preventive Measures

The principle of prevention is to optimize peripartum immune function, principally through management to encourage feed intake during the transition period (Cook

and Nordlund, 2004). It has been stated that poor nutritional management of dairy cows particularly before and after calving leads to metabolic disorders, which predisposes the cows to gynecological disorders, thereby reducing reproductive efficiency. Poor nutrition results in hypocalcaemia, high non esterified fatty acids and triacylglycerol; these are considered as the risk factors for endometritis (Roche, 2006). In particular prepartum diet should include 0.3ppm Selenium (ideally 5mg/day, Hogan *et al.*, 1993) and 1000-2000 IU/Cow/Day of Vitamin E (Weiss, 1998; Baldi *et al.*, 2000). The prepartum injection of Vitamin E may help to prevent retention of placenta (Bourne *et al.*, 2007). It is suggested that among animals with sub optimal circulating Vitamin E during the last week prepartum, an injection of 300 IU Tocopherol S/C one week before expected calving reduces the risk of retained placenta and subsequent uterine infections (Le Blanc *et al.*, 2002c). Selenium injections and oral Vitamin E supplementation prepartum reduces the postpartum uterine involution time (Harrison *et al.*, 1986), as well as high energy consumption during the last weeks of dry period might reduce the disease risk at parturition. Administration of a controlled released monensin capsule which release monensin at 335 mg/day for 95 days at cessation of lactation has reduced the incidence of postpartum gynecological disorders and monensin also increases the body condition score at calving (Melendez *et al.*, 2006). Usually healthy cows clear bacteria from uterus within approximately 3 weeks after calving and complete involution of uterus and cervix within 4-6 weeks. Endometritis may be prevented by paying attention to hygiene of cattle accommodation and calving facilities in terms of cleaner surface for animals to lie on, less contamination of skin and hair of animals with bacteria (Sheldon *et al.*, 2008; Azwai, 2008). Clean calving areas increase the reproductive efficiency in herd (Dargatz *et al.*, 2004). Managerial practices influenced the incidences of retained placenta and uterine infection, services per conception, percentage of herd open more than 100 days (Coleman *et al.*, 1985). Adequate cow comfort, cow management and nutrition, aggressive postpartum health monitoring program with preventive and curative measures to mitigate the negative effects of diseases reduces the incidence of reproductive disease (Santos *et al.*, 2010). It is well understood that calving complications cause reduced reproductive performance resulting in longer period between calving and conception. Retained placenta, metabolic disorders and cow parity are strongly correlated with development of postpartum endometritis in dairy herds (Kim and Kang, 2003). Cows calving during warmest months, on average, were seen in estrus 24 days sooner, received first service 42 days sooner and conceived 27 days sooner than cows calving during coldest months of the year (Etherington *et al.*, 1985). Oxytetracycline or Chlorhexidine solution is suggested to be infused in uterus of cows with purulent vulvar discharge 2 or more weeks postpartum

(Snider, 1984). The use of 30 IU of oxytocin for reduction of placental retention and subsequent endometritis (Mollo *et al.*, 1997) as well as use of uterine pessary containing Penicillin, Streptomycin, Formosulphathiazole, Ethinyloestradiol reduces the frequency and severity of uterine infections in cows after parturition (Dobson and Noakes, 1990). Administration of GnRH on day 14 postpartum will stimulate the reproductive physiology and assists in cleansing the uterus and bringing faster uterine involution thereby improving fertility and conception rate (Refsdal, 2000). The weekly IM administration of levamisole (2.5 mg/kg) starting from 5-6 weeks prepartum until 2 weeks prior to expected calving reduced the risk of pathological vaginal discharge in treated cows (Pancarci *et al.*, 2009). A recent study evaluated the efficacy of vaccinating pregnant heifers with inactivated bacterial components and/or protein subunits of *E.Coli*, *Fusiformis necrophorous* and *Trueperella pyogenes* on the subsequent occurrence of postpartum uterine diseases (Machado *et al.*, 2014). In general vaccination induced a significant increase in serum IgG titres against all antigens, with subcutaneous vaccination being more effective. However unless more trials on a larger number of cows are available such approaches cannot be currently suggested.

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