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Bilal Ahmad Ganaie
Ph. D Scholar, Division of Animal Reproduction, Gynaecology and Obstetrics, ICAR National Dairy Research Institute, Karnal, Haryana, India

Faheem Sultan
Ph. D Scholar, Department of pharmacology and toxicology, GADVASU Ludhiana, Punjab, India

Rouf Rashid Dar
Assistant Professor, Department of Veterinary Gynaecology and Obstetrics, IIVER Rohtak Haryana, India

Firdous Ahmad Baba
Ph. D Scholar, Department of Livestock Production and Management, SKUAST-K, Jammu, Jammu and Kashmir, India

Susheel Kumar
M.V.Sc, Division of Animal Reproduction, Gynaecology and Obstetrics, ICAR National Dairy Research Institute, Karnal, Haryana, India

Correspondence
Bilal Ahmad Ganaie
Ph. D Scholar, Division of Animal Reproduction, Gynaecology and Obstetrics, ICAR National Dairy Research Institute, Karnal, Haryana, India

Uterine infection in dairy animals and its ameliorative measures: A review

Bilal Ahmad Ganaie, Faheem Sultan, Rouf Rashid Dar, Firdous Ahmad Baba and Susheel Kumar

Abstract
Infertility is regarded as one of the major reasons for reduced life-time milk production in dairy animals. The causes of infertility in dairy animals are many and are complex, among which post-partum uterine infection alone accounts to around 25-30 per cent. A healthy uterine environment is supposed to be the main determinant for good fertility as any sort of damage to endometrium can disturb the normal reproductive functions leading to infertility. The development of uterine infection is determined by the immune status and execution of the same against the infectious agent, number/load of bacteria and its virulence. Uterine infection may prolong the time of uterine involution, resumption of first postpartum estrus, increases the number of services per conception, number of days open and incurs a huge economic drainage to the dairy industry. From the current literature it is quite evident that the uterine infections not only affect the milk production but also have negative impact on the ovarian follicular development and steroid production, expression of estrus and ultimately the conception thereby prolonging the intercalving interval. Keeping in view all the above facts, the following review provides a better understanding of uterine infections and developing effective preventive measures for minimizing the incidence of uterine infections in dairy animals.

Keywords: Infertility, uterine infection, endometrium, ovary, uterus

Introduction
In dairy animals the risk of uterine infections increases around peripartum period due to impairment in immune status. Compared to other stages of reproductive cycle, the prevalence of uterine infections around peripartum period is high [1].Within first week following parturition in almost 90 to 100 per cent of dairy cattle, contamination of the uterine lumen with bacteria occurs [2, 3]. These include both aerobic and anaerobic bacteria such as *Pseudomonas aerogenosa*, *Escherichia coli*, *Arcanobacterium pyogenes*, *Pasterulla multocida*, *Staphylococcus aureus*, *Prevotella species* and *Fusobacterium* species [4]. These causative agents get spontaneously eliminated within 2-4 weeks of parturition [5]. However, around 25-30 per cent of animals fail to expel these microbial agents, show a persistent inflammatory response and endometrial damage and are often infertile [3, 6].
The maintenance of an adequate uterine health that permits for timely resumption of ovarian activity following calving is a key component for bovine reproductive efficiency. [3, 7]. About 25-30 per cent of cows fail to expel the causative agents and develop metritis within 3 weeks following parturition [3, 8]. A similar proportion of cows have clinical endometritis (CE) within 3 weeks of calving [9, 10], but about 26 -74 per cent develop subclinical endometritis between 40-60 days in milk [11, 12]. Further it has been reported that with endometritis a decline in conception rate by a factor of 20 per cent occurs. These infections (both metritis and endometritis) in turn lead to increased days open, decreased conception rate, increased culling rate, increases number of services per conception and subsequently a huge economic drainage to the dairy industry [13]. Due to disruption of uterine and ovarian activity with these infections a better understanding of the interaction between uterine infections and application of preventive measures would help in amelioration of infertility in dairy animals.

Classification of uterine infections
Postpartum uterine infections have been classified as puerperal metritis/acute metritis/toxic metritis/septic metritis, clinical endometritis, subclinical endometritis and pyometra. The clinical definitions as proposed by Sheldon *et al*., (2006) [14] for common postpartum uterine infections are as under.
Puerperal metritis is defined as an acute illness with general systemic signs due to uterine infection. The disease is characterised by an abnormally enlarged uterus with a fetid watery

reddish brown to viscous purulent discharge in association with decreased milk yield, in- appetence, dullness and fever ≥39.5^0 C within 21 days of calving. In severe cases the affected animal shows anorexia, reduced milk yield, dullness, cold extremities, increased heartbeat, apparent dehydration, depression and sometimes animal may finally collapse.

Clinical metritis affected animal exhibits no systemic signs of illness, but have an abnormally enlarged uterus with purulent discharge within 21 days of calving.

Clinical endometritis is characterised by purulent (>50% pus) or mucopurulent (approximately 50% pus, 50% mucus) uterine discharge detectable in vagina within 21 days or more postpartum and without systemic signs of illness.

Subclinical endometritis is characterised by inflammation of the endometrial lining of the uterus and absence of any purulent material in the vagina. This condition results in a significant reduction in the reproductive performance with absence of clinical signs of the disease. This condition is usually diagnosed by evaluating the uterine cytology/ flushing samples for the proportion of polymorphonuclear cells.

Pyometra is characterised by the distension of uterus due to presence of purulent or mucopurulent material within its lumen, in the presence of an active corpus luteum and closed cervix. For post calving development of pyometra, the presence of infectious nidus within the endometrium is must [15]. This infectious nidus will prevent normal process of corpus luteum lysis by inhibiting the release of prostaglandin. Pyometra is considered a sub-set of endometritis wherein dairy cows ovulate even, in the presence of a contaminated uterus.

Incidence of uterine infection

Sharma *et al.* (1993) [16] have reported that around 18-40 per cent of dairy animals in India are culled due to infertility. Drillich *et al.* (2006) [17]; Benzaquen *et al.* (2007) [18] have reported that about 18.5% to 21% of dairy animals are affected by metritis with signs of systemic illness such as pyrexia. Similarly, the incidence of clinical endometritis ranges between 5.0 - > 30% [12, 19]. Among all uterine infections of dairy animals subclinical endometritis is most prevalent affecting about 30% of animals [10]. Kumari *et al.* (2016) [20] have reported in crossbred and Zebu cattle an incidence of metritis around 22.56% and 10.32% respectively. In buffaloes the incidence of uterine infection has been reported to be higher compared to cattle. In India, Rao and Sreemannarayana, (1983) [21]; Sar*et al.* (1996) [22] and Rao, (1982) [23] have reported an incidence of uterine infection, metritis and endometritis 24.7%, 25% and 30% respectively. An overall incidence of about 9.66% of uterine infection has been reported in buffaloes by Kumari *et al.* (2016) [20] in an organised dairy farm in India.

Pathogenesis of uterine diseases

Following calving in most of the animals a wide range of bacteria gain access to the uterine lumen via patent cervix. However, the main determinants of clinical disease are host immunity; bacterial load and pathogenicity of the bacteria and cleanliness of the environment where the actual calving occurs. The risk factors such as twins, dystocia, stillbirth and retained placenta shift the balance between these determinants more in favour of disease [24, 25]. However in order to minimize the chances of occurrences of uterine disease unluckily, these above mentioned factors are notliable to brought into account for intervention and the factors that could be actually addressed, such as cleanliness of the animal or environment, are believed to be less important [4].

The most prevalent bacteria isolated from the uterine lumen of dairy animals having uterine disease are *Escherichia coli* and *Arcanobacterium pyogenes* followed by a range of anaerobic bacteria such as *Prevotella* spp., *Fusobacterium necrophorum*, and *Fusobacterium nucleatum* [26] Bacteria have been also isolated from the uteri of animals free from any sort of clinical disease. Williams *et al.* (2005) [26] have reported that the *Staphylococci* and α-haemolytic *Streptococci* (both coagulase negative) presence within uterine lumen decrease the risk of endometritis. So, there are likely chances that in near future the probiotics may be considered for prevention/amelioration of disease. Six virulence factors of *E. coli* have been reported to be associated with uterine infection: fimH, astA, cdt, kpsMII, ibeA and hlyA. Following uterine infection with *E. coli*, the chances for subsequent infection with other bacterial agents or viruses increases [26, 27]. The prevalent virulence factor of E. *coli* associated with cows having metritis has been reported to be fimH.

Besides *E. coli*, *A. pyogenes* have been reported to be the main causative agent associated with endometrial damage and infertility [28]. Virulence gene plo expression have been reported from all the *A. pyogenes* strains isolated from the uterus, Silva *et al.* (2008) [29], which encodes for pyolysin [30]. The pyolysin (Cholesterol dependent cytotoxin) molecules aggregate at the cholesterol-rich domains of cell membranes and lead to pore formation, subsequently osmotic death of the cell [30]. Further, it has been reported by Miller. (2009) [31] that the in vitro addition of pyolysin to epithelial and stromal cells cultures readily kills them. Further, A. pyogenes produces a growth factor for *F. necrophorum*, thus supporting its disease causing potential. More ever, synergistic action of *A. pyogenes*, *F. necrophorum* and *Prevotella* species can enhance the chances of occurrence and severity of uterine disease [15]. Besides this, *F. necrophorum* produces a toxin called leukotoxin; *P. melaninogenicus* produces phagocytosis inhibiting substance [1].Trauma to the tissues during parturition, necrotic lochia associated with retained placenta provides an excellent media for bacterial attachment and invasion and subsequently growth. Thus, apart from host factors, virulence factors and number/load of bacteria are critical in determining whether an infection of postpartum uterus would establish itself as inflammatory conditions like clinical or subclinical endometritis.

Economic importance of uterine infection

In India, a clear estimate on the losses associated with uterine infection is not available but, a significant amount of economic losses can be minimised by proper management, proper diagnosis and timely treatment of uterine infections. The extra expenses due to uterine disease result from infertility, increased culling rate, losses from milk production, and the cost of treatment. A decline by 15 per cent and 12 per cent in milk production has been reported from cattle and buffaloes respectively due to uterine infections. Dubuc *et al.* (2011a) [32] have reported a per day loss of milk production by a factor of 3.7 in multiparous cows affected with metritis. Drillich *et al.* (2001) [33] have reported about €292 economic cost for a single case of metritis. Due to reproductive parameters alone, an estimated loss of $2.5 to $3 per cow per day has been reported from compromised reproductive efficiency beyond 100 days postpartum [34].

Uterine infection and ovarian function

It has been reported by Williams *et al*. (2007) [2] that the cows

that were having postpartum uterine infection, had delayed/slower growth of the first postpartum dominant follicle, lower circulating concentrations of plasma estradiol for the maximal follicle diameter, and in those animals that did actually ovulate, circulating concentrations of plasma progesterone were lower(< 2 vs> 5 ng/ml) 5 to 7 days post ovulation. PAMPs or inflammatory mediators compromise ovarian activity by acting on the hypothalamus, pituitary or ovary.

For postpartum resumption of ovarian cycles normal hypothalamic and pituitary functioning is critical. In animals with uterine infection ovarian follicular waves arise during first few weeks post parturition as follicle stimulating hormone (FSH) concentrations remain unaffected in such animals [35]. However, in sheep it has been reported by Karsch *et al.* (2002) [36] that *E. coli* derived LPS (endotoxin) suppresses GnRH and LH release from hypothalamus and pituitary gland respectively, and the sensitivity of the pituitary to gonadotrophin releasing hormone, thereby reducing the ability of dominant follicle to ovulate. A similar finding has been reported from dairy cattle by Peter *et al*. (1989) [37] post administration of LPS.

Recent studies have revealed that the gram negative bacteria derived lipopolysaccharide compromise the steroid production from granulosa cells of follicles. Presence of higher amount of LPS in the follicular fluid of uterine infection affected animals reduce the aromatase expression. Even low concentration of LPS in follicular fluid has been reported to supress the trancriptions of CYP17 and P450 arom enzymes necessary for steriodogenesis. Further, Magataa *et al*. (2014) [38] has reported that the LPS in follicular fluid might be the factor responsible for follicular atresia. Plasma circulating concentration of estrogen remains lower in these animals and subsequently less likely to ovulate due to weak estrogen positive feedback to the LH. Even in presence of LPS, if cows somehow manage to ovulate, the CL formed will be of smaller size and secreting lower amount of progesterone. Proinflammatory cytokines like IL-1, 2, 8, TNF, IFN-γ produced in response to bacterial associated molecular patterns may disturb normal luteal cell steriodogenesis. Further due to shift from $PGF_{2\alpha}$ (luteolytic) to PGE_2 (anti-inflammatory) luteolysis is disrupted, since the endometrial epithelial cells of animals affected with uterine disease secrete PGE_2 instead of $PGF_{2\alpha}$. This shift from $PGF_{2\alpha}$ to PGE_2 leads to extended luteal phases and hence infertility.

Preventive measures

Losses associated with uterine infections lead to a huge economic drainage to the dairy industry. But unfortunately, a very little progress has been made in this area, to have a control or prevent the same. So, a better understanding of its pathogenesis and application of control/ preventive strategies will prove to be of great practical and economic importance. Even though there is a huge disagreement regarding the treatment strategies of postpartum uterine infections, but there is a strong coherence among the researchers on the various measures necessary to prevent their occurrence [19, 39]. With due attention paid to dry cow nutrition and management, most postpartum problems can be prevented and which in turn can result in an improved pregnancy rate, reduced mortality, and very less chances of similarly related diseases [40, 41].

Prepartum feeding and health care

Huzzy*et al*. (2007) [19] has reported that near the time of calving, a low feed and water intake increases the incidence of postpartum metritis. So, one of the most effective and economical ways to avoid postpartum uterine infections is by ensuring high dry matter intake in the transition period. To be disease free, dairy cows are supposed to have a good body condition and not to lose body weight around peripartum period, as poor body condition has been shown to suppress immunity making them more susceptible to postpartum infections [42]. Further, an adequate level of vitamins and minerals in body tissues are must so as to maintain proper uterine health. There is a mixed belief regarding the association of body condition score and development of postpartum uterine infections. A poor body condition of dairy cows near calving time is associated with higher chances of dystocia, metabolic disturbances, retained fetal membranes and subsequently developing endometritis [43]. Dairy cows in over-conditioned state (BCS >4 on a 5 point scale) have been shown to exhibit a higher incidence of dystocia, poor uterine muscle tone, earlier attainment of fatigue during calving and consequently an increased risk of uterine infection [44, 45]. A body condition score of ≤ 2.5 is associated with high risk of development of uterine infections [45]. So, body condition scores of about 3.5 in late lactation and during transition is considered optimum, as dairy cows with such score are having little chances of developing the postpartum infection [46]. A marked loss of body condition from the dry period to near calving time is associated with an increased incidence of postpartum metabolic and reproductive problems.

Peripartum care

A due care is to be paid to common calving related problems like dystocia and its common risk factors and uterine inertia. Dairy cows with such problems are to be handled properly by well trained and qualified personnel so that damage to the genital organs is minimised. The risk for development of postpartum complications increases with improper handling of these cases by untrained and unqualified personnel. Retained placenta is regarded as one of the major risk factors for the postpartum development of uterine infection. Retained fetal membranes predispose dairy cows to different peripartum diseases including metritis, mastitis, ketosis, decreases the milk yield and resistance to diseases. But unfortunately due to its multifactorial aetiology, a universally acceptable preventive strategy cannot be effective [47]. Factors that compromise the immune status of animal during late pregnancy and early postpartum period predisposes them to development of retained fetal membranes [41]. Stress associated with parturition lead to increase in cortisol level due to which a reduced accumulation of leucocytes occurs within the placentomes, subsequently causing failure in expulsion of fetal membranes [48]. Further, it has been reported that insufficient prepartum provision of vitamin E and selenium is associated with high risk of retained fetal membranes [49]. Deficiency of Vitamin E results in reduced activity of glutathione peroxidase due to which lipid peroxidase content may increase and the synthesis of $PGF_{2\alpha}$ may be lowered, thus affecting myometrial activities [41, 50].The reproductive consequences of retained fetal membranes include an increase in days open, increase in service period, increase in calving to conception interval and subsequently increase in calving interval. Therefore, a preventive strategy which aim to accelerate placental expulsion from the uterine cavity and reduce chances of uterine bacterial contamination may prove beneficial in preventing cases of RFMs and hence, reducing uterine infection [48, 51].The probability of ketosis incidence increases

by a factor of 16.4 with retained fetal membranes [52]. Further, it has been reported that a cow having milk fever is 4 and 2.3 times more likely to develop retained fetal membranes and left abomasal development, respectively. Therefore, it is quite clear that in order to have a better postpartum fertility, incidence of postpartum metabolic diseases is to be kept within the permissible limit, as these diseases are believed to increase the incidence of postpartum metritis in dairy animals.

For the prevention of uterine infection many antimicrobial, hormonal therapies, ecbolics (like ergometrine) and certain immunomodulators have proven to be beneficial. Treatment of dairy cows with $PGF_{2\alpha}$ within first few hours of parturition has been effective in the prevention of RFMs, as $PGF_{2\alpha}$ has been reported to increase uterine contraction and myometrial activities [53]. Due to the uterotonic activity prostaglandins support the myometrium contractions and hence prevent chances of uterine infection by expulsion of fetal membranes [54]. Further it has been reported that dairy cows treated with $PGF_{2\alpha}$ are having an improved oestrus detection efficiency, shorter first service interval, and reduced days open [55]. Dairy cows that had been treated with intra uterine pessaries containing penicillin, streptomycin formo-sulphathiazole and ethinyl-oestradiol in the immediate postpartum period had a significant reduction in the number of cases infected with *A. pyogenes* and in those showing purulent discharge (Dobsons and Noakes, 1990). It has been reported by Goshen and Shpigel. (2006) [56] in heifers, that with post-calving intrauterine use of chlortetracycline, there has been a significant reduction in the detrimental effects of uterine infections. Further, Galvao. (2009) [12] reported that with an intrauterine infusion of ceftiofur hydrochloride there has been a significant reduction in the prevalence of clinical endometritis. Dairy cows that had been affected with RFMs following assisted calving, on intra uterine treatment with a combination of entrofloxacine and penicillin G had a reduced incidence of metritis [57]. Dairy cows that were having signs of pyrexia during the early postpartum period had a significant decrease in the incidence of metritis on treatment with ceftiofur hydrochloride [58].

Post-partum follow up

In managing reproductive performance the management practices which aim to prevent the postpartum disease are very important. The main focus of postpartum follow up should be to have early detection of post-partum diseases by regular and frequent monitoring and observations rather than to diagnose when it becomes clinical, which is more costly to treat and takes a long time to recover. In order to have early detection of problematic cows monitoring of rectal temperature during the first 10 days of postpartum is to be strictly monitored. Based on rectal temperature and visual signs (dull, depressed and alert) decision for further rectal or vaginal evaluation is to be taken accordingly. A well-established therapeutic protocol can be framed based on the outcome/finding of these evaluation criteria. Monitoring of body temperature and behaviour of animal are currently in practice in addressing retained fetal membranes and metritis in dairy cows. A systemic antibiotic is to be administered if the body temperature of cow exceeds 39.5^0C. NSAIDS along with broad spectrum antibiotics has been found to be more efficacious when deemed necessary based on evaluation criteria. Further, the incidence of postpartum uterine infections has been reported to be affected by the general farm hygiene, especially on beddings and maternity stalls [59, 60]. Plontzke *et al.* (2010) [61] have reported an increased incidence of uterine infections in cows that calved in stalls (O'Connor, 2009) [42] vs. those calving on pastures. Therefore, a high standard of calving hygiene is to be maintained so as to reduce the incidence of uterine infections.

Conclusion

In dairy animals postpartum uterine diseases are common disorders that negatively affect production and reproductive performance. This in turn incurs a huge economic drainage to the dairy industry by diminishing profitability and sustainability of dairy operations. Therefore, the need to look into the mitigating factors is high lightened and thereby minimising losses. Cows that had calved recently should be clinically examined by well qualified personnel so as to have early detection of those animals that are suspected to develop the disease. Further dairy farmers should take timely suggestions from nutritional experts and should adopt strategies on feeding management particularly during the transitional period. Proper maintenance of dairy animals, provision of clean and dust free area, proper breeding hygiene, early identification and treatment of dairy animals affected with subclinical /clinical form of disease is to be indicated to prevent / minimize the losses associated with uterine infections.

Conflict of interest

The authors declare that they have competing interests.

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