

Postpartum Uterine Diseases; Diagnostic Approaches and Management in Farm Animals; A Review

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Abstract

Postpartum uterine infections result from uterine contamination with bacteria during parturition. The postpartum environment of the uterine lumen supports the growth of a variety of aerobic and anaerobic bacteria. There are a number of risk factors for post-partum uterine disease in dairy cattle; cows having dystocia, retained placenta, twins or stillbirths and various metabolic disorders are more likely to develop uterine disease. Inflammation of the uterus slows down the process of involution in the uterus and delays the onset of activities of the ovaries leading to economic loss due to systemic illness, loss of milk and meat production and marked drop in fertility. Pyometra, metritis, clinical and subclinical endometritis are some of the most important illnesses during the postpartum period. A variety of methods such as uterine palpation, ultrasonographic features of the uterus, vaginoscopy, endometrial cytology, uterine culture, and uterine biopsy has been reported to identify postpartum diseases. Prevention of postpartum uterine disease would be better than cure, for both the animals and the economy. Thus, early diagnosis or predictions of uterine infections are important for effective postpartum management.

Key words: diagnosis; farm animals; postpartum; treatment; uterine infection

List of Abbreviations

RP: Retained placenta

RFM: Retained fetal membrane

DMI: Dry-matter intake

NEFA: Non-esterified fatty acids

AI: Artificial insemination

PAM: Pathogen associated molecules

E coli: Escherichia coli

PMN: Polymorphonuclear

GnRH: Gonadotropin releasing hormone

NSAIDS: Nonsteroidal anti-inflammatory drugs

1. Introduction

Postpartum period is defined as the period after parturition and lasts until reproductive function is restored so that another pregnancy can occur (A. Sharma et al., 2022). This period is the most critical stage in the reproductive cycle of farm animals (Ali and Ahmed, 2015). In cattle, the postpartum period is associated with uterine tissue remodeling, restoration of

immunological homeostasis and resumption of ovarian cyclicity necessary for subsequent fertility (Raliou et al., 2019). There are four major events during this period which include: myometrial contractions and expulsion of secundus, endometrial repair, resumed ovarian function and elimination of bacterial contamination in the reproductive tract (A. Sharma et al., 2017).

Postpartum uterine infection is extremely important in dairy cattle. It is both common and detrimental to reproductive performance (Hossain et al., 2015). A healthy or slightly inflamed uterus will clear pathogenic bacteria and keep its normal state by means of defense mechanisms during the first four to six weeks after parturition (Sheldon et al., 2008). Clearance of bacteria depends on various factors, such as uterine involution, uterine contractions, innate and adaptive immunity, and regeneration rate of the endometrium (Rosales and Ametaj, 2021).

Uterine infections are common disorders affecting dairy cows during the postpartum period, when these protective barriers of uterus are breached (Vidya et al., 2022). The majority of postpartum inflammatory conditions of the uterus begin with bacterial contamination of the uterine lumen (Sheldon et al., 2006). Relaxation of the vulva and cervical dilation during parturition allow for the entrance of bacteria into the uterus, therefore, bacterial contamination of the uterus postpartum is common (Farhad Ghasemi, 2011). Uterine health and the expression of clinical uterine infection in the postpartum period depends on balance between factors such as the animal,

immunity, the number and pathogenicity of the microbes, and the uterine environment (Vallejo-Timaran et al., 2021, Sheldon et al., 2008).

Postpartum uterine diseases are important for animal welfare and economic reasons, causing cow discomfort, elimination from the herd and impaired reproductive performance (Machado, 2015). Inflammation of the uterus slows down the process of involution in the uterus and delays the onset of activities of the ovaries leading to economic loss due to systemic illness, loss of milk and meat production and marked drop in fertility (Deori and Phookan, 2015, Negasee KA, 2020). Postpartum uterine infections can also delay the regeneration of endometrium and disrupt the resumption of cyclic ovarian function which leads to the postponement of first insemination (AI), increase in number of inseminations per conception and thus calving interval is prolonged (A. Sharma et al., 2018). These complications are also responsible for slower uterine involution, reduced reproductive rate, prolonged inter conception and calving interval, cost of medication, drop in milk production, reduced calf drop, and early depreciation of potentially useful cows (Hossain et al., 2015, Ganaie et al., 2018). The financial losses associated with uterine infection are dependent on the cost of treatment, reduced milk yield, and infertility (Sheldon et al., 2008).

The aim of this review is to assess different postpartum uterine diseases, causes, consequences, and highlight update on different diagnostic and therapeutic measures in farm animals.

2. Major Risk factors for postpartum uterine diseases

There are several risk factors that contribute to postpartum uterine contamination or physical damage of the uterine tissue; among them the major factors, such as retained placenta (RP), calving

abnormalities (dystocia, twins, and stillbirth), angle of the vulva, and parity (Machado, 2015); and also, various metabolic disorders are more likely to develop uterine disease in animals (Williams, 2013, Piersanti and Bromfield, 2022).

2.1. Retained placenta

Retained placenta (RP) is a uterine disease that occurs in the postpartum period and affects cows more frequently than other animal species (Rezende, E.V. et al., 2020). Retained placenta is a direct risk factor for postpartum reproductive and metabolic disorders (Kyung Han and Hwa Kim, 2005). Negative consequences related to RP are: delayed uterine involution, increased time to first insemination, increased number of services per pregnancy, decreased pregnancy rates and increased days open. Furthermore, RP has been associated with a significantly increased risk to suffer from clinical diseases like metritis, endometritis, ketosis and even mastitis (Geert, 2015).

2.2. Dystocia

Dystocia can be defined as the incapability of the cow to expel neonates through the birth canal from the uterus. This condition occurs because of problems with the maternal or fetal (Galma B., 2022). Dystocia is a risk factor that significantly increased the overall incidence of clinical metritis and endometritis after calving (Negasee KA, 2020, Kumar et al., 2019). Tissue trauma caused by dystocia most likely facilitates adhesion and invasion of the germs (Geert, 2015).

2.3. Nutritional and metabolic factors

Metabolic pressure after calving, negative energy balance and metabolic diseases such as ketosis increase the incidence of uterine disease (Molina-Coto and Lucy, 2018). Regarding the metabolic challenge, the transition period is characterized by a state of negative energy, mineral, and vitamin balance in which there is a decrease in dry-matter intake (DMI), leading to a sharp decrease in glucose, minerals (e.g. calcium, selenium) and vitamins (e.g. A and E) right after parturition, and an increase in body fat mobilization in the form of non-esterified fatty acids (NEFA; this state of negative energy, mineral, and vitamin balance leads to immunosuppression (Galvão, 2013).

Decreased postpartum levels of blood minerals are associated with uterine diseases, and hypocalcaemia after parturition was associated with higher incidences of metritis and clinical endometritis (Machado, 2015).

2.4. Other Managemental factors

Management factors and complications at parturition can increase the incidence of uterine disease (Molina-Coto and Lucy, 2018). General farm hygiene, especially on beddings and maternity stalls, have been reported as affecting the incidence of postpartum uterine infections (Onyango, 2014). Management factors and complications at parturition such as calving assistance can increase the incidence of uterine disease and have been identified as risk factors for clinical and subclinical endometritis (Damarany, 2022).

3. Major pathogenic bacterial infection of the postpartum uterus

The postpartum environment of the uterine lumen supports the growth of a variety of aerobic and anaerobic bacteria (Sheldon et al., 2006, Deori and Phookan, 2015). The bacterial agents commonly isolated from postpartum uterus include: *Escherichia coli*, *Arcanobacterium pyogenes*, *Fusobacterium necrophorum*, *Bacteroides* species, *Staphylococcus* species, *Mannheimia haemolytica*, *Pasteurella*

species, *Haemophilus somnus*, *Pseudomonas aeruginosa*, *Clostridium* species and *Streptococcus* species. Among these, *Arcanobacterium pyogenes*, coliforms and the Gram-negative anaerobes, *Fusobacterium* and *Bacteroides* species are commonly encountered (Deori and Phookan, 2015, Farhad Ghasemi, 2011, Piersanti and Bromfield, 2022, Rosales and Ametaj, 2021).

There is no doubt that uterine pathogens may negatively affect reproduction both by causing direct endometrial damage and by producing toxins. Bacterial colonization or growth within the uterine tissue releases endotoxins called pathogen associated molecules (PAM) (Molina-Coto and Lucy, 2018). Endotoxins, lipopolysaccharide component of gram-negative bacteria such as *E coli*, are released into the circulation during bacterial disintegration and induce fever, lethargy, tachycardia, and tachypnea (Hagman, 2022).

4. Common Post-Partum Uterine Disorders

4.1. Pyometra

Pyometra is characterized by the accumulation of purulent or muco-purulent material within the uterine lumen and distension of the uterus, in the presence of an active corpus luteum on ovary (Sheldon et al., 2006, A. Sharma et al., 2017, Galvão, 2012). Pyometra can happen if ovulation occurs too early in the post-partum period and corpus luteum is formed during uterine infection (Galma B., 2022). A closed cervix is common in most cows; however, in few cases, closure of the cervical lumen is not fully completed, and therefore, purulent discharge can be seen come out from the vagina when the cow lies down, urinates, or defecates (Amin YA et al., 2021).

4.2. Metritis

Metritis is a severe inflammatory response that occurs within all the layers of the uterus including the endometrium, sub mucosa, myometrium and perimetrium (A. Sharma et al., 2017). It is most commonly occurring in the postpartum period of dairy cattle within 10-14 days after parturition (Asker, 2021). Postpartum metritis usually associated with uterine inertia, twin births, RFM, prolonged manipulations and injuries to the vulva and/ or birth canal (Deori and Phookan, 2015, Mohammad Rahim Ahmadi et al., 2023, Machado, 2015).

Puerperal metritis is an acute systemic illness due to infection of the uterus with bacteria, usually within 10 days after parturition (Sheldon et al., 2006). Puerperal metritis is characterized by the following clinical signs: a fetid red-brown watery uterine discharge and, usually, pyrexia; in severe cases, reduced milk yield, dullness, inappetence or anorexia, elevated heart rate,

and apparent dehydration may also be present (Sheldon et al., 2009, Azawi, 2008).

Toxic puerperal metritis (i.e. acute septic metritis) is characterized by increased rectal temperature, depression, anorexia, fetid watery vulvar discharge. Toxic puerperal metritis can be a severe problem, and uterine infections that are life-threatening (Azawi, 2008).

4.3. Endometritis

Endometritis is inflammation of the functional lining of the uterus, called the endometrium (Negasee KA, 2020). It is defined as inflammation of the endometrium after 21 days postpartum without systemic signs of illness, and can be considered the chronic stage of uterine inflammation. Endometritis has been classified as clinical or subclinical (Machado, 2015).

4.3.1. Clinical endometritis

Clinical endometritis has been defined as local inflammation of the endometrium, and commonly associated with presence of purulent or mucopurulent material, containing >50% pus, in the vagina at or more than 21 days after calving (Rosales and Ametaj, 2021; Sheldon et al., 2009; Lima, 2018). There are risk factors related to clinical endometritis in dairy cows such as hygiene of the perineum at the time of calving, peripartum metabolic status, parity, retained fetal membranes, delivery of twins and dystocia (Mohammad Rahim Ahmadi et al., 2023).

4.3.2. Sub-clinical endometritis

Subclinical endometritis is a uterine disease that does not present clinical signs and cannot be easily diagnosed on farm site. But as a form of uterine disease, it is producing deleterious effects on reproduction in dairy cows (Molina-Coto and Lucy, 2018). Subclinical endometritis has also been described as 'cytological endometritis' and is defined as "an increased proportion of PMN in endometrial cytology samples obtained by endometrial cytobrush or low-volume uterine lavage (Priest, 2013, Negasee KA, 2020; Damarany, 2022; Moges N., 2018).

5. General Diagnostic Approaches to Postpartum Uterine Diseases

5.1. Rectal palpation

Among commonly used diagnostic tools, rectal palpation is probably the most common method for diagnosing uterine infections (Negasee KA, 2020). The purpose of the trans-rectal palpation is to detect pathological changes in the uterus consistent with endometritis, such as a general enlargement, fluctuating contents and a hardened uterine wall (Linda H, 2020).

5.2. Examination of Vagina and vaginal discharges

Vaginal discharge can be scored and used as an indicator of uterine infection (Lewis, 1997). In practice, the examination of the contents of the vagina for the presence of pus is the most useful procedure for diagnosis of uterine infection (Sheldon et al., 2008). The diagnosis of metritis and clinical endometritis should include an inspection of the contents of the female genital tract by speculum or insertion of a clean-gloved-hand into the vagina (Sheldon and Owens, 2017). Vaginoscopy has been considered as more sensitive method than simple external inspection for detection of purulent discharge (Kumar et al., 2019).

5.3. Ultrasonography

Ultrasonography has become an important diagnostic tool for evaluating the female reproductive system (Kumar et al., 2019). The use of trans-rectal ultrasonography permits more objective measurement of the diameter of the uterine horns and cervix, and visualization of mucus and pus within the uterine lumen (Sheldon et al., 2006). The Ultrasonographic appearance of abnormal uterine fluid can vary from anechoic fluid with floating particles (referred to as 'snowy specks') to homogenous, purulent exudates that can

appear similar to the echogenicity of the surrounding uterus (Honparkhe et al., 2021).

5.4. Cytology

Uterine cytology is the collection and counting of cells obtained from the uterus, and has become the standard to which other techniques are compared. Uterine cytology makes it possible to quantify inflammatory cells (Priest, 2013). The proportion of neutrophils is counted and then used to assess the degree of uterine inflammation. Cytological samples can be collected either with uterine lavage or a cytobrush. The cytobrush gives an in-situ sample which may represent the inflammatory status of the endometrium (Linda H, 2020).

5.5. Uterine biopsy

Endometrial biopsy is highly diagnostic for pathology and has potential to generate extensive quantitative data on physiologic or immune mechanisms in cows if genomic and proteomic data can be obtained from the same biopsy material (Chapwanya et al., 2010). Biopsy provides detailed information about uterine health status (Madoz, et al., 2014).

When biopsy technique is used, pieces of endometrial tissue are taken by using biopsy forceps; all these techniques require laboratory work for evaluation of the uterine samples (Hossain et al., 2015).

5.6. Bacterial culture

A uterine culture is an essential tool to determine the etiology of uterine infection. A swab is the most accurate means of obtaining samples for identification of the specific and non-specific bacteria that cause infection. A true uterine culture should be taken from the uterus without contamination by extraneous bacteria (Azawi, 2008). Uterine fluids can be swabbed and cultured to characterize the anaerobic and aerobic bacterial populations during the postpartum period (Lewis, 1997).

6. Management and Treatment Measures for Postpartum Uterine Diseases

An effective control of post-partum contamination of the uterus provides the chance to improve both fertility and general health condition of dairy herds. Since postpartum uterine diseases are very costly (Billy, 2009); Prevention and early treatment of postpartum uterine infections are more economical than treatment at a later stage when diseases get established (Dolezel et al., 2010). Thus, early diagnosis or predictions of uterine infections are important for effective postpartum management (Manimaran, et al., 2016, Bilby et al., 2009).

6.1. Management Practices

The occurrence of uterine infections can be reduced by minimizing the need for assistance at calving through prenatal knowledge of twin birth, calf sex and oversized calves. Calving assistance should only be carried out when necessary and appropriate hygiene should be used to decrease the incidence of uterine infections (El-Khadrawy et al., 2015). Generally, it is believed that disinfection of calving equipment's, frequent replacement of beddings and general hygiene of the calving environment can help minimize cases of uterine infections (Onyango, 2014).

6.2. Nutrient supplementation

Prevention of uterine disease requires appropriate nutritional management during the transition period and after calving (Sheldon et al., 2009). Trace mineral and vitamin deficiency early postpartum, particularly selenium and vitamin E have long been identified as a cause of uterine disease, and because of the importance of energy balance on the incidence of uterine disease, nutritional supplements that prevent ketosis may be an important component for the prevention of uterine diseases (Galvão, 2013).

6.3. Hormonal treatments

Drug compounds, such as estrogens, luteolytic prostaglandins, and gonadotropin releasing hormone (GnRH) have been used in the postpartum period alone or in conjunction with other agents to treat retained fetal membranes (RFM), metritis, and Pyometra (Olson et al., 1985, Smith, 2009). The effect of these compounds on uterine motility and defense mechanisms makes them useful treatment alternatives to antimicrobial agents. PGF₂ α is not only luteolytic but also appears to have pro-inflammatory actions that might enhance neutrophil function. The treatment of choice of Pyometra in cows is administration of prostaglandin F₂ α or its analogues at normal luteolytic doses (Susan E, 2016).

Estrogen may stimulate uterine tone to evacuate abnormal uterine contents, increase production of mucus that contains host defense compounds and induce estrus, thereby reduce progesterone levels markedly stimulate neutrophil phagocytosis and resistance of the uterus to infection (El-Khadrawy et al., 2015).

6.4. Anti-inflammatory drugs

Studies have shown that NSAIDs provide therapeutic effects such as analgesia, ovarian function recovery, and prevention and treatment of uterine inflammation (Cui et al., 2021, Galvão, 2013). Treatment of postpartum inflammation with nonsteroidal anti-inflammatory drugs (NSAIDs) has had varying success due to differences in efficacy with drug choice, mode of action (i.e., cyclooxygenase or prostaglandin-endoperoxide synthase 1 or 2 inhibition), as well as timing and duration of treatment (Crookenden, 2023).

6.5. Antibiotic Therapy

The success of uterine infection treatment depends on evacuation of the uterine fluids, response of the infectious agents to the used drug, concentration and frequency of drug use and the exposure of the entire endometrium to the treatments (Mohamed A Gohar et al., 2018).

Systemic and local treatments have been used to treat uterine diseases (Molina-Coto and Lucy, 2018). The systemic antimicrobial therapy must be used to treat the cases of RFM, metritis and pyometra while intrauterine treatment is preferred treatment of choice for endometritis as it is local inflammation and does not result in systemic illness (Honparkhe et al., 2021). Antibiotics commonly used for the treatment of puerperal metritis include penicillin, third-generation cephalosporins, or a combination of ampicillin with Oxytetracycline or cloxacillin (Asker et al., 2021, Haimerl et al., 2016, Susan E, 2016).

Alternatives for the treatment of endometritis caused by Gram negatives that are resistant to gentamicin include amikacin sulfate, polymyxin B, neomycin sulfate, ampicillin, carbenicillin, and kanamycin sulfate. The broad-spectrum antibiotics ceftiofur and ticarcillin, with or without clavulanic acid, are also commonly used in mares (Pyörälä, 2014).

6.6. Intrauterine treatment

In contrast to systemic administration, intrauterine administration achieves higher drug concentration in the endometrium, but little penetration to deeper layers of the uterus or other genital tissues (Stephen J, 2008). Local treatment involving intrauterine antibiotic infusion aims to produce an even distribution of an active drug throughout all layers of the uterus, limited systemic absorption, low tissue irritation, and high antibacterial activity within the uterine environment. Antiseptic agents, such as iodine, chlorhexidine, and saline, have been infused into the uterus, but there have been few studies to

determine the efficacy of these compounds on postpartum metritis (Smith, 2009). Intrauterine infusion of a 50% dextrose solution has proven to be effective in treating uterine diseases (A. Sharma et al., 2022).

7. Conclusion

Uterine infection is one of the commonest causes of poor fertility. They are also responsible for, economic loss due to systemic illness, loss of milk and

meat production, cost of medication and poor welfare. There are complex multifactorial causes and a wide range of factors contributes to their disease's occurrence. The main risk factors for uterine diseases are primiparity (for metritis only), dystocia, male offspring, twins, stillbirth, abortion, prolapsed uterus, retained placenta (RP). Antibiotics, hormonal treatment with estrogens, PGF₂ α , and GnRH, NSAIDs and intrauterine medications are commonly used in treating uterine infections. Good peripartum management and accurate diagnosis are critical to facilitate the use of the most effective treatment and limit the negative impact of postpartum uterine disease on fertility. Thus, Prevention and early treatment of postpartum uterine infections are more economical than treatment at a later stage when diseases get established.

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