**Review Article**

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# Postpartum uterine infection & ovarian dysfunction

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**Postpartum uterine infections such as metritis, endometritis and mastitis have been considered as underlying causes for ovarian dysfunction in mammals. Almost all mammals, particularly dairy animals are susceptible to postpartum uterine infections, resulting in impaired fertility and economic loss. One of the factors for low fertility in females is ovarian dysfunction, which is exhibited as impaired growth and function of ovarian follicles by the postpartum infection. Immune system of mammals provides a host defence mechanism against pathogenic microbes through the recognition of pathogen-associated molecular patterns (PAMPs) and forming inflammasomes. Like immune cells, ovarian granulosa cells also exhibit a similar pattern of cytokine gene expressions on exposure to PAMPs. Genome-wide transcriptomic approaches explored the molecular mechanisms underlying the immune function of buffalo granulosa cells during endotoxin exposure. Understanding the molecular mechanism of ovarian dysfunction due to uterine infection would be helpful to implement various strategies to handle the adverse effects of postpartum uterine disease on fertility by developing potential therapeutics. Therefore, this article focuses on key factors that are responsible for postpartum infection and particularly summarizes the molecular mechanism of infection underlying the ovarian dysfunction in dairy animals.**

**Key words** Endotoxin - granulosa cells - ovarian dysfunction - postpartum period - toll-like receptors - uterine infection

## Introduction

Reproductive health performance in mammals is mainly influenced by various postpartum uterine diseases such as metritis, endometritis and mastitis. Postpartum uterine disease is a global problem with higher prevalence in animals. The uterine diseases are mainly caused by infectious pathogenic bacteria in dairy animals. The identified pathogenic bacteria associated with endometritis and other uterine diseases are *Arcanobacterium pyogenes*, *Escherichia coli*, *Fusobacterium necrophorum* and *Prevotella melaninogenicus* species[1]. The severity of uterine infection depends on the kind of pathogens, genetic factors and immune response of animals[2]. In general, the uterus of animals is exposed to bacteria during calving and harbours the bacteria at least for two-week postpartum. Such a bacterial or microbial load in the uterus affects the ovarian cyclicity, resulting in acyclicity, infertility and prolonged calving intervals, if the animals could not combat the infection[1].

Persistent uterine infection reduces immune efficiency[3] in buffalo cows. Consequently, the uterine functions such as harbouring spermatozoa and proper embryonic development would be

compromised[4]. In addition, the uterine infection affects hypothalamic-pituitary-ovarian axis, thereby dysregulates the ovarian follicle development, ovulation and corpus luteal function[5-7]. Primarily, the bacterial infection inhibits the estradiol production resulting in the slow growth of ovarian-dominant follicles and decreases the number of ovulation events which leads to low productivity[8] and high economic loss.

The animal body non-specifically responds to all kinds of pathogens through its natural innate immune system. This non-specific response is mediated through acute-phase proteins, such as $\alpha_1$-acid glycoprotein (AGP), serum amyloid A (SAA) and haptoglobin, which are induced by pro-inflammatory cytokines[9]. Acute-phase proteins are sensitive innate immune molecules and inflammation indicators of many diseases, including uterine infection during postpartum. The rising incidence of postpartum uterine infections generated an interest in understanding the molecular mechanisms behind the diseases that impact the animal fertility. Therefore, this review was focused on different aspects of postpartum uterine infection as well as its related ovarian dysfunctions.

**Postpartum period**

Postpartum period is the period between one parturition to the next pregnancy. During this period, the female reproductive system undergoes at least four dynamic events, the involution of uterus, renewing of endometrium, resumption of ovarian cyclic activity and clearance of bacterial contamination from the reproductive tract[8]. During involution of the uterus, the uterus size is reduced by the shrinkage and contractions of uterine smooth muscles, loss of caruncles and endometrial regeneration. These events of uterine involution can be delayed by several factors such as the difficulty in parturition, low calcium levels, presence of placental remnants and the inflammation of uterine layers such as endometrium and metrium[10].

The regeneration of endometrium generally happens in three to four weeks during postpartum period. During this period, the endometrium is remodelled to its normal architechture[10] from the damaged condition, which usually occurs during parturition. If the regeneration events are delayed, the endometrium is inflamed. If the inflammation is prolonged and untreated, it results in endometriosis, which consequently leads to premature ovarian failure and ovarian dysfunction.

Resumption of ovarian cyclicity or the presence of ovarian dysfunction depends on the resumption of normal endocrine milieu. Primarily, the circulating estradiol levels are important to resume the normal ovarian cyclicity. However, the circulatory estradiol levels will be low during the early days of postpartum due to inhibitory effect of uterine infection on steroidogenesis[2]. Due to low circulatory estradiol levels, the plasma follicle-stimulating hormone (FSH) concentrations will be increased, to resume the ovarian follicular dynamics by maintaining the recurrent increase of the FSH levels for every 7-10 days[11]. In addition to the resumption of FSH dynamics, the luteinizing hormone (LH) pulse frequency is also important to determine the fate of dominant follicle whether it would ovulate or not. Usually, insufficient LH pulse frequency and low ovarian follicular estradiol levels delay the resumption of ovarian cyclicty[12].

During parturition, the mammalian uterus gets contaminated with a wide spectrum of microbes. Majorly, aerobic and anaerobic Gram-positive as well as Gram-negative bacteria such as *E. coli*, *Corynebacterium pyogenes*, *Streptococcus*, *Staphylococcus*, *Pseudomonas* and *Bacillus* were found to be present in the uterus during early postpartum[2]. In addition, other microbes including virus, fungi and mycoplasma were also found to be responsible for uterine infections during postpartum. To resume normal reproductive functions, the uterus needs to clear the microbial contamination during postpartum. If animals cannot clear the microbial contamination from the uterus, the uterine layers would be inflamed and lead to post-parturient disorders, such as metritis, submetritis, endometritis and mastitis[4]. Due to infection, the uterine wall, its underlying glandular tissues and the muscular layer get inflamed, and such inflammation is called metritis[13]. Endometritis is the inflammation of functional inner lining of the uterus[4,14]. Both metritis and endometritis generally do not show the systemic signs[15]. The incidence of these reproductive disorders varies in different dairy animals. Occurrence of metritis, clinical endometritis and subclinical endometritis ranged from 10 to 20 per cent[16]. These reproductive disorders may also reduce the milk yield and cause mammary gland infection called mastitis[17]. All these disorders are dependent on the immune system of animals, species, microbial load and type[6]. Most of the bacteria contaminate the uterine lumen and are removed by different host defence mechanisms. Failure of the animal defence mechanism and aggravated

infection by these organisms are the major contributors to endometritis and infertility[18,19].

**Postpartum uterine infections cause ovarian dysfunction**

Ovarian cyclic events such as the development of follicles, oocyte release and formation of corpus luteum are the key components for fertility attainment and maintenance of reproductive performance in mammals. These ovarian cyclic events are regulated by hypothalamus, pituitary and other endocrine glands with their tissue-specific and temporally expressed factors. Uterine bacterial infection causing postpartum uterine diseases of dairy animals disrupts the regulation of the key ovarian events[20]. There was a difference in the microbial population between postpartum normal and endometritic uteri which was evident by a metagenomic analysis with 16S rRNA in buffaloes[21]. The pathogenic organisms mainly Gram-negative bacteria initially attach to the uterine mucosal layer, disrupt the epithelium, penetrate to submucosa and release their secretary molecules such as lipopolysaccharide (LPS). The LPS then enters into ovarian follicular fluid through circulation and disturb the ovarian cyclic events. The endotoxin responsible for inhibition of ovarian dominant follicle growth and ovarian steroidogenesis is mainly responsible for the infertility in animals[20,22,23].

**Molecular mechanism of host response to postpartum uterine infection**

The molecules such as acute phase proteins, Toll-like receptors (TLRs) and antimicrobial peptides (AMPs) play important roles in the innate immune system. These molecules trigger the recognition of microbial pathogens in host and respond to microbial challenge during infection[24]. For instance, TLR4 interacts with bacterial pathogen-associated molecular patterns (PAMPs) such as endotoxins, specific DNA and lipids and elicits the cellular response in terms of pro-inflammatory cytokines, chemokines and AMPs, which mediate either inflammation or tolerance[25]. Inflammation is a pathophysiological situation which serves as a protective mechanism against pathological offences.

Pathogenic microbes cause inflammation through PAMPs. Bacterial PAMPs could be either secretary in nature or present on the surface. For example, Gram-negative bacteria present their PAMPs as LPS, an endotoxin, on their outer membrane. These microbial PAMPs interact with mammalian cells through specific receptors called TLRs. Mammalian genome encodes many TLR genes to interact with a wide range of PAMPs and protect the cells[25,26]. For example, the TLR1, TLR2 and TLR6 can interact with bacterial lipids such as lipoteichoic acid. The TLR3, TLR7, TLR8 and TLR9 could bind to bacterial or viral nucleic acids. The classical TLR is TLR4, which interacts with bacterial LPS along with CD14 and MD2 molecules. The TLR5 and TLR9 were found to interact with flagellin and bacterial DNA, respectively. The binding of TLRs with PAMPs triggers a signal transduction pathway, which activates the transcription and translation of pro-inflammatory cytokines and chemokines, the molecules that could attract the other immune cells towards the site of infection[26,27].

Ovarian granulosa cells like immune cells were also found to show phagocytosis phenomenon and the expression of TLRs[28]. As these cells could express the TLRs, they have the ability to interact with bacterial PAMPs, like LPS, and secrete inflammatory cytokines. During this immune response, the granulosa cells were observed to compromise their primary function of steroidogenesis[29]. It has been reported that LPS decreases the estradiol production by downregulating the *CYP19A1*, a gene encoding aromatase enzyme to catalyze the rate-limiting step in E2 biosynthesis[30]. The downregulation of the *CYP19A1* leads to slow follicular development and ovarian dysfunction. Similarly, a key group of PAMPs that can reach intracellular compartments could activate inflammasomes and help in the release of interleukin-1 beta (IL-1β)[31]. In many species, the IL-1β is known to be involved in the ovulation event as well as in the suppression of the *CYP19A1* gene expression and estrogen biosynthesis in granulosa cells[32]. As granulosa cells have a crucial role in estrogen biosynthesis as well as to nurture the oocytes before ovulation, impairment of their function due to postpartum uterine infection shows a reduction in fertility and lowers the conception rates at subsequent breeding procedures[23].

The lower pregnancy rates are also dependent on the progesterone levels. The immunity of endometrium is under the control of estradiol, progesterone, somatotrophins and local regulatory proteins production[8]. However, when endometrium loses its barrier function due to bacterial infection[33], its prostaglandin secretion would be shifted from F to E series, which prevents the luteolysis resulting in extended luteal phase. Hence, some animals show prolonged anestrus intervals during postpartum. On the

contrary, the levels of progesterone would be less due to infection, thereby the pregnancy rates may be low.

**Acute phase proteins and anti-microbial peptides: Biomarkers for postpartum uterine infection**

Acute-phase proteins can be used as biomarkers for the prediction of postpartum uterine infections. During the first few weeks of postpartum in cows, increased levels of peripheral plasma concentrations of pro-inflammatory cytokines lead to an increase in the production of acute phase proteins by the liver[34]. For instance, increased pro-inflammatory cytokines, like tumour necrosis factor alpha (TNFα), act on the liver hepatocytes and enhance the production of acute phase proteins, such as $\alpha_1$-AGP, SAA and haptoglobin[34]. This is one of the mechanisms to provide defence against the systemic and local bacterial infections in the uterus. Acute-phase proteins also act as biomarkers to predict the postpartum uterine infections. In cattle, of the nine acute-phase proteins, haptoglobin has been proved as a potential diagnostic and prognostic marker of enteritis, mastitis, pneumonia, peritonitis, endocarditis and endometritis[35]. Increased concentrations of haptoglobin were found in the serum after the onset of metritis during the first days of postpartum[36]. Along with haptoglobin levels, there were significant changes in the levels of α1-AGP both at the time of calving and postpartum endometritis in cows[37].

In addition to the acute-phase proteins, AMPs are secreted in response to the uterine infections. AMPs are the small peptides (<100 amino acids) having amphipathic conformation, which allows them to bind to the microbial membranes. AMPs are the broad-spectrum peptides which can act against Gram-positive and Gram-negative bacteria. These also possess antifungal as well as antiviral activities[38]. These are produced by the epithelial cells as well as phagocytic cells confronting microbes. Some of the AMPs have constitutive expression whereas others are only expressed during an injury or exposure to the microbes. Bovine uterine tissue has the expression of lingual antimicrobial peptide, bovine neutrophil β-defensins (BNBD4 and DEFB5), tracheal antimicrobial peptide and bovine β-defensins (BBD19, BBD123 and BBD124)[39]. The defensins bind to the negatively charged phospholipid membrane of the pathogens, inducing membrane depolarization and disrupting the integrity of their cell wall[40]. Overall, the increased levels of both acute-phase proteins and AMPs can be exploited as the potential biomarkers to predict postpartum uterine infections.

**Uterine infection and endotoxin tolerance**

In females, persistent uterine infections cause subfertility or infertility due to a compromised immune system during parturition. Endotoxin (LPSs) has been shown to accumulate in the ovarian follicular fluid during uterine and mammary gland infections. These endotoxins lead to ovarian dysfunction due to perturbed ovarian follicular growth and impaired function of the ovarian granulosa cells. Like innate immune cells, granulosa cells also express TLRs and perform phagocytosis[41]. According to the previous reports, endotoxins act as ligands to TLR4 present on the surface of granulosa cells[25]. This ligand-receptor interaction allows the initiation of a complex signalling mechanism, which activates pro-inflammatory cytokine production. The increased expression of pro-inflammatory cytokines is the crucial part of immune response required to fight against the pathogens. However, this response can be detrimental for the host which may lead to the dysfunctions causing the subsequent tissue damage, stress and, eventually death. To combat these inflammatory responses during infection, cells undergo various protective adaptations. One of the protective mechanisms is endotoxin tolerance (ET), an essential for maintaining immune-homeostatic balance. In this mechanism, the repeated exposure of the cells or organisms to the endotoxin (*e.g.* LPS) results into a transient unresponsive state. ET leads to the decrease in inflammatory cytokines gene expression such as TNF and IL-6, and induction in the expression of factors that mediate the resolution of inflammation, which leads to the dysregulation of immune response. The phenomenon of tolerance induction due to the endotoxin of Gram-negative bacteria (*E. coli*) has been shown *in vivo*[42] as well as *in vitro* in various cells, such as monocytes, macrophages and dendritic cells[43,44]. These studies provide new insights into the host molecular events responsible for the ET and also encourage to study further in granulosa cells which will help in developing potential therapeutics to treat impaired function of granulosa cells caused due to the persistent endotoxin in follicular fluids during uterine infection.

**Clinical significance/impact of postpartum uterine infection on fertility**

Postpartum uterine infections occur mostly in the high-yielding dairy animals. Previously, it was

reported that between 20 and 33 days of postpartum, cows affected with clinical endometritis were 1.7 times more prone to be culled as compared to cows without endometritis[16]. Another evidence showed that animals with postpartum metritis possessed reduced conception rate and took prolonged time for first insemination by 7.2 days, ultimately leading to subfertility[5]. It has also been reported that subclinical endometritis is the most common of all uterine diseases and affects approximately 30 per cent of the lactating dairy cows[45]. Hence, the increased proportion of the uterine diseases associated with impaired follicular function, decreased pregnancy rate per artificial insemination and extended period of pregnancy consequently lead to the infertility and thus economic losses[20].

The status of immune functionality of an animal during the peripartum period is significant in determining the probability to develop postpartum uterine disease. Furthermore, energy status in the peripartum period is one of the crucial determinants for the development of uterine disease. Endocrine and metabolic changes occurring during parturition, which can be a part of uterine defence mechanisms, may also be responsible for the uterine diseases in dairy animals. The invasion of neutrophils in the uterus is the first step of the innate immune response against uterine infection, which is determined by the pro-inflammatory cytokines and other factors. Impaired activation and chemotaxis of neutrophils just after calving is attributed to the decreased expression of inflammatory cytokines in the endometrium. This ultimately leads to the development of endometritis in cows[46]. Therefore, future work should focus on studying the detrimental effects of bacterial infection on ovarian functions along with the understanding of host response to the postpartum infections. Emerging knowledge about postpartum uterine infections will provide a platform for new therapeutic alternatives and treatment strategies for ovarian dysfunction.

## Conclusion

Understanding of molecular mechanisms behind postpartum uterine infections in dairy animals is essential to explain the causes of ovarian dysfunction. Uterine infections cause the impairment of ovarian function, which further leads to reduced conception rates and considerable infertility, affecting the profits of dairy industry. Uterine bacterial infections result in the delayed growth of dominant follicles in the ovary, reducing its ability to ovulate and, ultimately resulting in subfertility to infertility. Many studies on understanding the molecular mechanisms for ovarian dysfunction were conducted by targeting the model and predominant bacterial endotoxin, LPS, during uterine infections. The LPS is usually accumulated in ovarian follicular fluid during uterine infections. In the ovarian follicles, the granulosa cells recognize LPS through TLR4/CD14/LY96 (MD2) complex, which further reduces estradiol secretion through its classical signalling mechanisms. Understanding the molecular cues will help in the development of potential therapeutics to treat impaired granulosa cells' function during uterine infections. Therefore, the interactions between the uterine infection, immunity and reproduction need to be further studied along with the underlying mechanisms.

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