Research Article

COX-2 Expression, IL-6 Concentrations, and Endometrial Progesterone Receptor Immunolocalization in Bacteria-Induced Endometritis in *Rattus norvegicus*

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Abstract | Endometritis is an inflammatory disorder of the endometrium commonly caused by *Escherichia coli* (*E. coli*) and *Staphylococcus aureus (S. aureus)*. This condition is associated with elevated pro-inflammatory cytokines, altered progesterone receptor (PR) expression, and increased activity of cyclooxygenase-2 (COX-2). This study aimed to evaluate serum Interleukin-6 (IL-6) levels, endometrial PR immunolocalization, and COX-2 expression in bacterial-induced endometritis in *Rattus norvegicus* using different bacterial species and inoculation doses. Twenty-one rats were used for IL-6 analysis and assigned to six groups inoculated with *E. coli*, *S. aureus*, or both at 1.5×10^5 or 1.5×10^8 CFU/mL. Blood samples were collected 36 hours post-inoculation and analyzed using ELISA. For PR and COX-2 assessment, 21 progesterone-primed rats were divided into seven groups: negative control, single-bacteria induction, and mixed-bacteria induction at both doses. Uterine tissues were collected 36 hours after treatment and examined using immunohistochemistry with evaluated using the Immunoreactive Score (IRS). Statistical analyses included ANOVA for IL-6 and Kruskal–Wallis followed by Mann–Whitney U tests for PR and COX-2. High-dose bacterial inoculation (1.5×10^8 CFU/mL) significantly increased IL-6 levels ($P < 0.05$). PR expression was markedly reduced in rats treated with *S. aureus* and mixed bacteria at high doses, whereas low-dose groups showed no significant differences from controls. COX-2 expression increased in all bacteria-treated groups, with the strongest staining observed in mixed-bacteria inoculation at 1.5×10^8 CFU/mL. In conclusion, high-dose bacterial induction induces a strong inflammatory response, characterized by elevated IL-6, reduced PR expression, and increased COX-2 activity. These findings support the use of high-dose single or mixed bacterial inoculation as a reliable experimental model of endometritis in rats.

Keywords | Bacterial inoculation model, COX-2, Endometritis, IL-6, Progesterone receptor

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INTRODUCTION

Endometritis is an inflammatory disorder of the endometrium and is recognized as a major cause of infertility in female livestock, particularly cattle. This condition may present as either clinical or subclinical endometritis, with the latter occurring more frequently after parturition and often without visible clinical signs.

Clinical endometritis is characterized by the presence of purulent, whitish, yellowish, or mucopurulent discharge with a foul odor, while subclinical endometritis lacks these outward manifestations (Budiyanto *et al*., 2016). Both conditions can lead to temporary or permanent reproductive impairment, ultimately affecting the reproductive efficiency and productivity of animals (Fazil *et al*., 2019).

The development of endometritis is closely associated with poor environmental hygiene and the presence of opportunistic pathogens. Several non-specific bacteria have been identified as causative agents of uterine infections, including *Streptococcus* spp., *Staphylococcus* spp., *E. coli*, and Corynebacterium pyogenes (Sinaga *et al*., 2021). *S. aureus* has been reported as a dominant pathogen in the reproductive tract of Aceh cattle, with a prevalence of 66.66% (Hajar *et al*., 2018), whereas E. coli is another significant uterine pathogen, accounting for 30% of isolates in Aceh cattle (Rafika *et al*., 2020). Similar findings have been reported globally, where *S. aureus* contributes to 21.8% and *E. coli* to 48.3% of endometritis cases, respectively (Liu *et al*., 2013; Raheel *et al*., 2020). Uterine infection may also occur secondary to dystocia, uterine prolapse, retained placenta, or unhygienic management practices (Thasmi *et al*., 2018). The prevalence of endometritis in Indonesia is notably high, ranging from 20% to 40% (Mamas *et al*., 2018).

Endometritis not only affects uterine health but also causes substantial economic losses due to reduced milk yield and impaired reproductive performance (Gilbert *et al*., 2005). Infertility in affected animals is often associated with persistently elevated progesterone levels. This result from the failure of the uterus to release prostaglandin F2α (PGF2α) necessary for corpus luteum (CL) regression (Mamas *et al*., 2018). Under normal physiological conditions, PGF2α is released on days 16–18 of the estrous cycle to lyse the CL (Melia *et al*., 2013). Progesterone, produced by the CL, plays an essential role in preparing the uterus for pregnancy (Djojosoebagio, 1990), and its action depends on the presence of progesterone receptors (PR), which are distributed within the epithelial and stromal cells of the endometrium (Patel *et al*., 2014). Therefore, alterations in PR expression may serve as important indicators of uterine health, fertility status, and therapeutic response in endometritis cases.

A key immunological parameter associated with uterine infection is interleukin-6 (IL-6), a pro-inflammatory cytokine involved in innate immune activation and tissue defense (Hidayat and Parawansa, 2021). IL-6 is produced by various cell types, including endothelial cells, leukocytes, macrophages, fibroblasts, and uterine epithelial cells, particularly in response to tissue injury or bacterial invasion (Dwi *et al*., 2013; Puspita *et al*., 2017). Elevated IL-6 levels are strongly correlated with the severity of inflammation and tissue damage, making it a valuable biomarker in inflammatory diseases (Tania *et al*., 2014; Setiawan *et al*., 2014). Despite the established relevance of IL-6 in inflammatory processes, comprehensive reports on IL-6 dynamics in rodent models of endometritis induced with *E. coli* and *S. aureus* at varying bacterial concentrations remain limited.

Several studies have also reported increased COX-2 expression in cases of endometritis caused by *E. coli* and *S. aureus*. Jana *et al*. (2009) observed a marked upregulation of COX-2 in the porcine endometrium following *E. coli* induction, with significantly higher expression in severe acute endometritis compared with mild acute cases. Similarly, Mitacek *et al*. (2020) demonstrated that the proportion of COX-2–positive in the endometrium of dogs with endometritis was significantly elevated relative to healthy uterine tissue. This increase reflects the underlying pathophysiological processes that characterize inflammatory conditions of the uterus, in which COX-2 is rapidly induced as part of the host inflammatory response.

Given the importance of inflammatory markers and hormonal regulation in the pathophysiology of endometritis, research on COX-2 expression, IL-6 expression, and progesterone receptor alterations provides an integrated approach to understanding disease mechanisms. To address these gaps, the present study was designed to analyze COX-2 expression, serum IL-6 levels, and evaluate progesterone receptor expression in the endometrium of Rattus norvegicus experimentally infected with *E. coli*, *S. aureus*, or their combination at different inoculation concentrations. Immunohistochemistry (IHC) was employed to determine COX-2 and PR expression, offering insights into uterine receptivity and hormonal dysregulation under inflammatory conditions.

MATERIALS AND METHODS

Animals and experimental design

Female *Rattus norvegicus* aged 3–4 months and weighing 160–200 g were used in this study. All animals were acclimatized for 14 days under controlled environmental conditions and provided ad libitum access to a commercial diet (T29-4) and drinking water. A completely randomized design was applied, consisting of seven treatment groups with three rats in each group. To ensure uniform reproductive status, all rats received subcutaneous progesterone at a dose of 16 mg/kg BW once daily for five consecutive days before induction.

Bacterial preparation and induction of endometritis

After hormonal priming, the rats were randomly assigned

to seven experimental groups. Animals were allocated into seven experimental groups: K0 (negative control), K1–K3 (low-dose treatment groups), and K4–K6 (high-dose treatment groups). Each group received treatments according to the designated dosage levels as described below.

A negative control receiving physiological saline (K0), groups induced with *E. coli* at 1.5×10^5 or 1.5×10^8 CFU/mL (K1 or K3), groups induced with *S. aureus* at 1.5×10^5 or 1.5×10^8 CFU/mL (K2 or K4), and groups induced with a combination of *E. coli* and *S. aureus* at both concentrations (K5 or K6). Bacterial induction was performed on the fifth day after progesterone administration.

Rats were anesthetized intraperitoneally using ketamine (10 mg/kg BW) and xylazine (50 mg/kg BW). After shaving and aseptic preparation, a midline incision was made along the *linea alba* to expose the uterine horns. The bacterial suspension was injected into the right uterine horn according to group allocation. The incision was then sutured using vicryl, and the animals were allowed to recover. This procedure followed the method of Demirel et al. (2019) with necessary modifications.

Blood collection and measurement of interleukin-6

Blood samples were collected 36 hours after bacterial induction from the retro-orbital venous plexus. Approximately 3 mL of blood was obtained and centrifuged at 3,500 rpm for five minutes to separate serum. Interleukin-6 (IL-6) levels were analyzed using a BIOENZY ELISA kit following the manufacturer's protocol. Standards and samples were added to the microplate wells, followed by anti–IL-6 antibody, streptavidin–HRP, substrate solutions, and a stop solution. The optical density was measured at 450 nm within 10 minutes after the final reaction step.

Tissue collection and histological preparation

At the termination of the experiment, the rats were euthanized by cervical dislocation. Uterine tissues were collected, fixed in 10% neutral buffered formalin, dehydrated in graded ethanol, cleared in xylene, and embedded in paraffin. Tissue blocks were sectioned at 4 µm thickness using a rotary microtome, mounted on poly-L-lysine–coated slides, and subsequently prepared for immunohistochemical analysis.

Immunohistochemical detection of COX-2 expression and progesterone receptors

Immunohistochemical staining was conducted using a mouse and rabbit specific HRP/DAB detection kit. Tissue sections were deparaffinized, rehydrated through descending ethanol concentrations, rinsed in running water and PBS, and treated with hydrogen peroxide to block endogenous peroxidase. Nonspecific binding was blocked prior to incubation with the primary antibody against the progesterone receptor for approximately 1.5 hours at room temperature.

Sections were then incubated with a biotinylated secondary antibody, followed by streptavidin–peroxidase. DAB chromogen was applied to visualize antigen–antibody binding. Counterstaining was performed using Mayer's hematoxylin before dehydration, clearing, and mounting with Entellan®. Slides were examined under a light microscope at 400× magnification.

Evaluation of COX-2 and progesterone receptor expression

Progesterone receptor (PR) expression was identified by brown DAB staining in the nuclei and cytoplasm of endometrial cells. Staining intensity was assessed in five representative fields per slide using the Immunoreactive Score (IRS). method described by Vermeirsch *et al.* (2002) and Saruhan *et al.* (2011), which categorizes staining as absent (0), weak (1), moderate (2), or strong (3).

Statistical analysis

Interleukin-6 data were analyzed using one-way analysis of variance (ANOVA) followed by Duncan's post-hoc analysis was used to assess statistical differences among groups, whereas immunohistochemical intensity scores were examined using the Kruskal–Wallis test followed by the Mann–Whitney U test for post-hoc comparisons. Statistical significance was set at $P < 0.05$.

ANOVA followed by Duncan's post-hoc analysis was used to assess statistical differences among groups.

RESULTS AND DISCUSSION

Positive COX-2 expression was detected in the endometrial samples of all treatment groups (K0–K6), whereas no immunoreactivity was observed in the negative control slide. The negative control (K–), which was processed without primary antibodies, served to confirm that the immunohistochemical (IHC) procedure followed the staining protocol provided in the IHC kit. COX-2 immunoexpression patterns for each group are presented in Figures 1, 2, and 3. Positive COX-2 expression was indicated by the presence of brown immunoreactive staining, reflecting the binding of anti–COX-2 antibodies to the COX-2 enzyme and subsequent chromogenic reaction with diaminobenzidine (DAB).

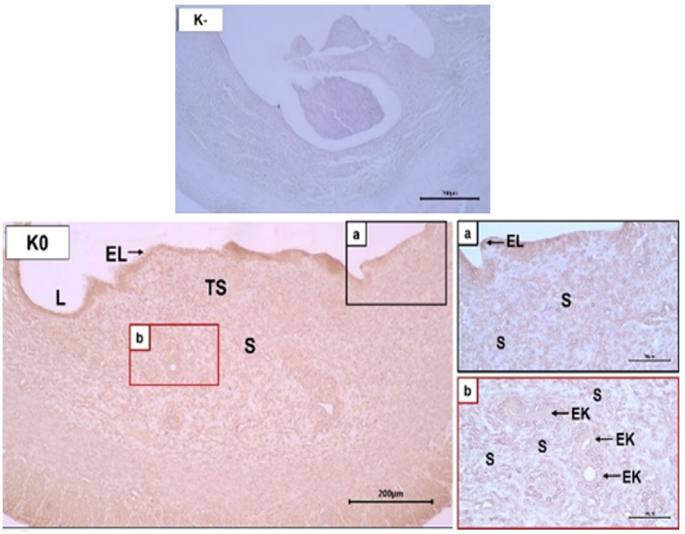

Figure 1: Representative photomicrographs showing COX-2 immunoreactivity in the uterine endometrium of control rats. (A) Negative staining control (K–) processed without primary antibody. (B) Negative treatment control (K0) inoculated with physiological saline. Scale bars: 200 µm (overview), 50 µm (inset). L: lumen, TS: tunica submucosa, EL: luminal epithelium, EK: glandular epithelium, S: stroma

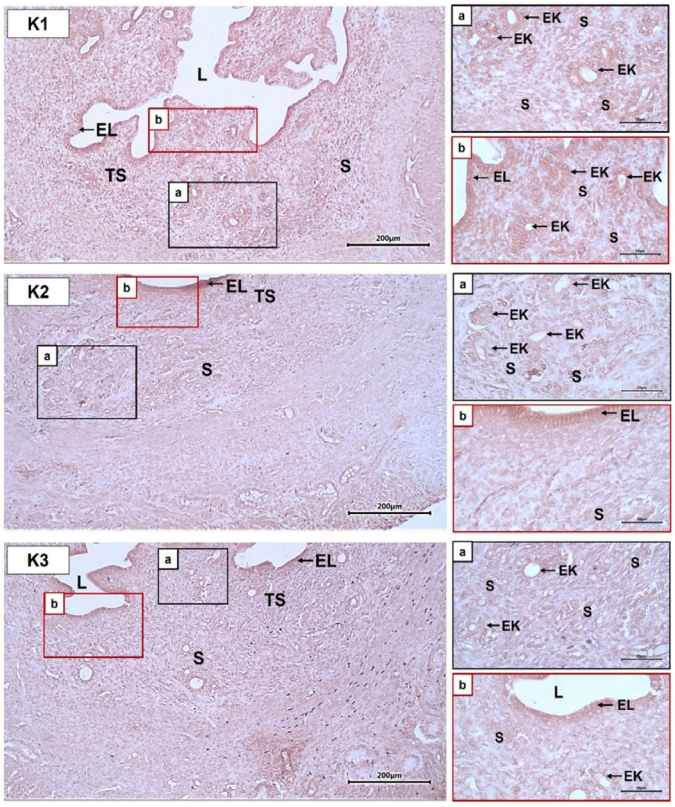

Figure 2: Representative photomicrographs showing COX-2 immunoreactivity in the uterine endometrium of treatments rats. K1 = *E. coli* 1.5 × 10^5 CFU/mL; K2 = *S. aureus* 1.5 × 10^5 CFU/mL; K3 = mixed *E. coli* + *S. aureus* 1.5 × 10^5 CFU/mL. IHC staining, scale bars: 200 µm and 50 µm.

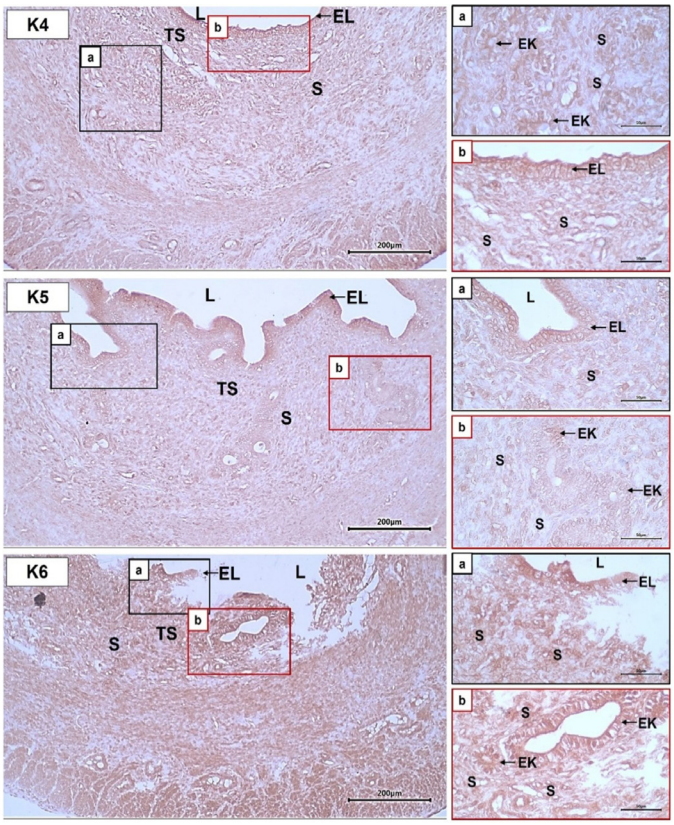

Figure 3: Representative photomicrographs showing COX-2 immunoreactivity in the uterine endometrium of treatments rats. K4= *E. coli* 1.5×10^8 CFU/mL; K5= *S. aureus* 1.5×10^8 CFU/mL; K6= mixed *E. coli* + *S. aureus* 1.5 × 10^8 CFU/mL. IHC staining, scale bars: 200 µm and 50 µm.

Across all treatment groups, COX-2 expression was observed in the luminal epithelium, glandular epithelium, and stromal cells, with the strongest immunoreactivity detected in stromal and epithelial compartments. These findings are consistent with Mitacek *et al.* (2020), who reported robust COX-2 expression in stromal, luminal, and glandular epithelial cells in canine endometritis. Upregulation of COX-2 is part of the normal inflammatory response, as cellular damage induced by bacterial infection triggers the release of inflammatory mediators such as cytokines and vascular endothelial growth factor (VEGF), which recruit immune cells and stimulate endometrial cells to synthesize COX-2 (Kumar, 2011).

Differences in IHC staining intensities were evaluated using the Immunoreactive Score (IRS) system (Table 1). Mean COX-2 expression scores for each treatment group are presented in Table 1.

The increased COX-2 expression likely results from bacterial-induced damage to endometrial epithelial, stromal, and glandular cells, which stimulates COX-2 activity as part of the inflammatory cascade. *E. coli* infection has been reported to cause structural damage to endometrial tissue (Sheldon *et al.*, 2009), while *S. aureus* produces toxins

Table 1: Mean (±SD) COX-2 expression in the endometrium, interleukin-6 concentrations, and progesterone receptor expression in the endometrium of rats induced with *S. aureus* and *E. coli* bacteria

Treatment group	COX-2 expression score (Mean ± SD)	IL-6 concentration (ng/mL; Mean ± SD)	Progesterone receptor expression (Mean ± SD)
K0 (NaCl)	1,27±0,12^{a}	na	1,27±0,31^{a}
K1 (*E. coli* 1,5x10^{5} CFU/mL)	1,8±0,35^{ab}	2.55±0.72^{a}	1,13±0,23^{a}
K2 (*S. aureus* 1,5x10^{5} CFU/mL)	1,67±0,31^{ab}	2.98±0.31^{ab}	1,20±0,20^{a}
K3 (*E. coli* and *S. aureus,* 1,5x10^{5} CFU/mL)	1,93±0,12^{b}	2.51±0.59^{a}	0,93±0,12^{ab}
K4 (*E. coli* 1,5x10^{8} CFU/mL)	2,53±0,12^{c}	4.59±1.38^{b}	1,00±0,20^{ab}
K5 (*S. aureus* 1,5x10^{8} CFU/mL)	2,4±0,2^{c}	4.87±1.74^{b}	0,60±0,20^{b}
K6 (*E. coli* and *S. aureus,* 1,5x10^{8} CFU/mL)	2,87±0,12^{d}	3.11±0.71^{ab}	0,80±0,00^{b}

Different superscripts indicate significant differences ($P < 0.05$).

capable of destroying host cells (Husna, 2018). Similarly, Ding *et al*. (2023) demonstrated that pathogenic bacterial infection induces inflammation characterized by oedema, pus accumulation, and apoptotic damage to uterine cells, ultimately compromising endometrial integrity.

Among all treatment groups, COX-2 expression was highest in K6, followed by K4 and K5, all of which received high-dose (1.5×10^{8} CFU/mL) bacterial inoculation. The severity of inflammation may be influenced by bacterial concentration, incubation time, and individual immune responses. Dar *et al*. (2016) reported that higher inoculation doses lead to more severe endometrial infection, supporting the findings of this study. Overall, inoculation with E. coli and S. aureus, either individually or in combination, at both low and high concentrations, effectively induced endometritis in rats and resulted in dose-dependent upregulation of COX-2 expression.

To evaluate the systemic inflammatory response induced by bacterial inoculation, serum IL-6 concentrations were measured in all experimental groups. The mean IL-6 levels in white rats inoculated with *E. coli*, *S. aureus*, or a combination of both at different bacterial concentrations are presented in Table 1.

Overall, animals inoculated with high bacterial concentrations (K4–K6) exhibited markedly higher IL-6 levels compared with those receiving low concentrations (K1–K3). Duncan's post-hoc analysis further confirmed that groups K4 and K5 had significantly elevated IL-6 concentrations compared with K1 and K2, indicating a dose-dependent inflammatory response.

The elevated IL-6 concentrations observed in the high-dose bacterial inoculation groups indicate that bacterial load plays a critical role in determining the severity of uterine inflammation. IL-6 is a key pro-inflammatory cytokine released as an early host response to pathogenic invasion, particularly by both Gram-negative and Gram-positive bacteria. Thus, these findings align with the report of Dar *et al*. (2016), who demonstrated that the intensity of infection increases proportionally with the inoculation dose.

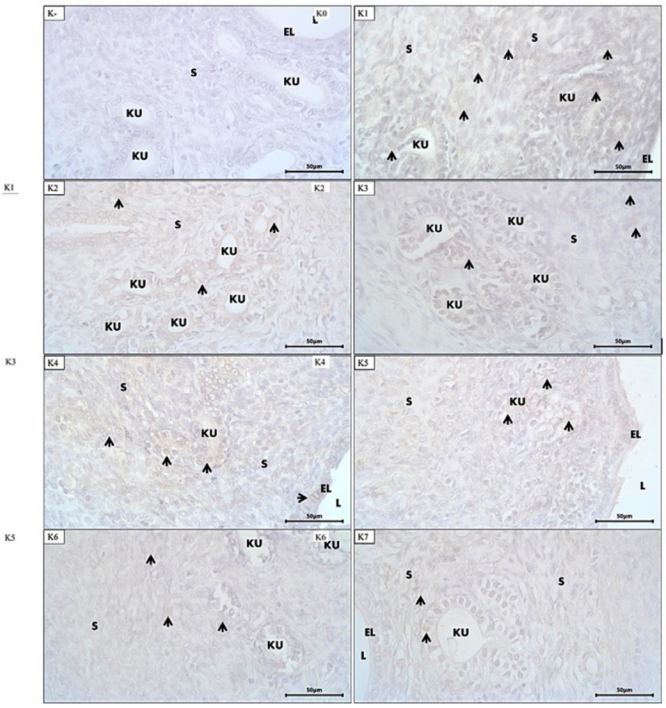

Figure 4: Distribution of progesterone receptors in the uterine endometrium of white rats. Negative control slide (K–); K0: negative treatment control; K1–K6: bacterial induction treatment groups. IHC staining, scale bar = 50 µm. Lumen (L), luminal epithelium (LE), stroma (S), uterine glands (KU).

Increased IL-6 levels during endometrial infection have also been documented in cattle and buffalo with endometritis, where pro-inflammatory cytokines are detected in serum, tissue, and uterine fluid (Loyi *et al*., 2013; Kim *et al*., 2014). Immune cell activation, along with stimulation of endometrial epithelial cells, triggers cytokine release aimed at eliminating invading pathogens (Xu *et al*., 2014). Therefore, IL-6 concentration may serve

as a sensitive indicator of uterine inflammation.

The comparatively higher IL-6 levels in the *S. aureus*-inoculated group may also be influenced by the surgical procedure, as S. aureus is a common pathogen in wound infections (Gallucci *et al*., 2009), thus, wound-related inflammatory responses may have contributed to the elevated IL-6 levels observed in this group.

To assess the effect of bacterial infection on uterine endocrine function, progesterone receptor expression was evaluated using immunohistochemistry. Positive immunolabeling was observed in the luminal epithelium, glandular epithelium, and stromal cells in all treatment groups, as shown in Figure 4. Brown immunostaining within the cytoplasm or nucleus indicated receptor expression, whereas the negative control showed no staining.

Groups inoculated with *S. aureus* 1.5 × 10^8 CFU/mL (K5) and the combined bacterial inoculum at the same concentration (K6) showed a significant decrease in progesterone receptor expression compared with the negative control (K0) and the low-dose inoculated groups (K1, K2) (Table 1). These findings suggest that high-dose bacterial infection adversely affects endometrial receptor integrity.

The decreased expression of progesterone receptors in the groups inoculated with *S. aureus* at 1.5 × 10^8 CFU/mL and in those receiving the high-dose bacterial combination indicates that bacterial infection directly compromises the structural and functional integrity of the endometrium. Toxins produced by pathogenic bacteria including lipopolysaccharide (LPS) from *E. coli* and hemolytic toxins from *S. aureus* are known to induce epithelial injury through oxidative stress, necrosis, and the activation of apoptotic pathways. Structural damage to the luminal epithelium, glandular epithelium, and stromal components leads to reduced receptor density and impaired cellular responsiveness to progesterone (Sheldon *et al*., 2009; Husna, 2018).

In addition to the direct effects of bacterial toxins, the intense inflammatory milieu contributes significantly to the downregulation of progesterone receptor expression. Elevated levels of proinflammatory cytokines such as IL-6 and TNF-α during severe endometritis may suppress progesterone receptor gene transcription through activation of the NF-κB signalling pathway, which is known to antagonize progesterone action (Ding *et al*., 2023). This condition is exacerbated by oedema, leukocyte infiltration, and destructive tissue remodelling. The accumulation of inflammatory cells and mediators disrupts the microarchitecture of the endometrium, ultimately compromising the ability of progesterone to regulate uterine proliferation and differentiation.

Physiologically, progesterone requires adequate receptor expression to maintain endometrial homeostasis, regulate uterine contractility, and support implantation processes. Thus, the decreased receptor expression observed in the high-dose infection groups reflects a substantial functional impairment. These findings are consistent with previous reports indicating that acute or chronic intrauterine infections may induce progesterone resistance, a condition in which uterine tissues fail to respond effectively to progesterone despite normal circulating levels. This phenomenon can interfere with fertility by impairing implantation or altering oestrous cycle dynamics.

No significant differences were observed among groups K1–K4, which were administered lower bacterial doses. This outcome may be attributed to several factors, including an inoculum dose that was insufficient to induce measurable tissue damage, as well as individual variation in immune resilience. As noted by Herath *et al*. (2009), animals with stronger innate and adaptive immune capacity may effectively limit infection despite being exposed to similar bacterial loads. The concepts of tolerance, resistance, and avoidance also help explain the variability in progesterone receptor expression among groups (Sheldon *et al*., 2019; Råberg *et al*., 2009). The endometrium is an immunologically active tissue equipped with intrinsic tolerance mechanisms to prevent excessive tissue injury when encountering specific pathogens (Jose and Brown, 2016).

Overall, the findings indicate that high-dose bacterial inoculation is more likely to induce marked endometrial damage, characterized by COX-2 expression, elevated IL-6 levels and reduced progesterone receptor expression. Therefore, inoculation with *S. aureus* at 1.5 × 10^8 CFU/mL, as well as a combination of *E. coli* and *S. aureus* at the same concentration, can be recommended as reliable experimental models of endometritis in *Rattus norvegicus*.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, high-dose bacterial induction induces a strong inflammatory response, characterized by elevated IL-6, reduced PR expression, and increased COX-2 activity. These findings support the use of high-dose single or mixed bacterial inoculation as a reliable experimental model of endometritis in rats.

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NOVELTY STATEMENT

This study offers a novel contribution by establishing an integrated biomarker-based rat model of bacterial endometritis, combining COX-2 immunoexpression, IL-6 upregulation, and progesterone receptor suppression as interconnected indicators of uterine inflammation. By employing both single-species and mixed *E. coli*, *S. aureus* infections at two inoculation strengths, the study identifies a clear dose-dependent pathological pattern and validates high-dose mixed bacterial challenge as a superior model. This framework provides new methodological value for pathophysiological and therapeutic investigations in reproductive inflammation.

AUTHOR'S CONTRIBUTION

Tongku Nizwan Siregar, Teuku Armansyah and Amalia Sutriana: Conceptualization; Teuku Armansyah, , Tongku Nizwan Siregar, Sri Wahyuni, Sultan Arif, Maulvi Nazir, and Intan Tridiva: Methodology, formal analysis, and investigation; Sri Wahyuni and Amalia Sutriana: data processing; Tongku Nizwan Siregar, Teuku Armansyah, Amalia Sutriana, Budianto Panjaitan, Sultan Arif, Maulvi Nazir, and Intan: Writing original draft preparation, writing review, and editing. All authors have read and agreed to the published version of the manuscript.

Generative AI and AI-assisted technology statement

The authors declare that generative AI and AI-assisted technologies were used in this study solely for the purpose of developing the research framework and improving the clarity and quality of the English language. The use of these tools was limited to language refinement and structural organization and did not involve data analysis, data interpretation, or the generation of scientific conclusions. The authors take full responsibility for the content, accuracy, and integrity of the manuscript.

Conflict of interest

The authors have declared no conflict of interest.

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