

REVIEW

General and comparative aspects of endometritis in domestic species: A review

O. Bogado Pascottini¹ | C. Aurich²  | G. England³ | A. Grahofer⁴ 

¹Department of Internal Medicine, Reproduction and Population Medicine, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

²Artificial Insemination and Embryo Transfer, Department for Small Animals and Horses, Vetmeduni Vienna, Vienna, Austria

³School of Veterinary Medicine and Science, University of Nottingham, Leicestershire, UK

⁴Clinic for Swine, Department for Clinical Veterinary Medicine, Vetsuisse Faculty, University of Bern, Bern, Switzerland

Correspondence

A. Grahofer, Clinic for Swine, Department for Clinical Veterinary Medicine, Vetsuisse Faculty, University of Bern, Bremgartenstrasse 109a, 3012 Bern, Switzerland.
Email: alexander.grahofer@unibe.ch

Abstract

Endometritis is a leading cause of sub- and infertility in domestic animal species. The healthy uterus is colonized by commensal bacteria, viruses and yeast/fungi that represent the nonpathogenic microbiota. A shift in the number or type of organisms accompanied by immune dysfunction, however, may trigger uterine infection and inflammation. Metritis is associated with inflammation of all uterine layers (endometrium, myometrium and perimetrium), whereas endometritis is a more superficial inflammation involving solely the endometrium. Endometritis generally occurs at two time points in domestic animal species, postpartum and postmating. Postpartum endometritis may chronically persist, either as a low-grade disease that often manifests as a vaginal discharge but not a systemic illness (in some species termed clinical endometritis) or sometimes subclinical where features are only detected by endometrial sampling. Contamination of the uterus at the time of mating occurs by direct deposition of semen (ejaculated or artificially inseminated) into the uterus. Improper drainage of the ejaculatory fluid or an inadequate immune response may result in persistent mating-induced endometritis. Both postpartum and postmating endometritis interferes with fertility by creating a suboptimal environment for embryo development and placentation, and chronic endometritis may have an impact on sperm survival and fertilization ability. In the postpartum animal, there may also be changes in milk production and maternal behaviour, which can affect offspring health and survival. Preventive strategies for endometritis largely depend on monitoring their known risk factors, which are sometimes specific with regard to the species. Effective, nonantibiotic therapy for endometritis is not available to date. Overall, extensive research has been performed in cattle and horses to unravel key aspects of endometritis, but in sows and bitches, the available literature is scant. Thus, the need and opportunity to investigate the condition vary considerably among domestic species and necessitate their comparative assessment. This article reviews general and comparative aspects of the diagnosis and classification, pathogenesis, preventive strategies and therapeutics of endometritis in domestic species with a specific focus on cows, mares, sows and bitches.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2023 The Authors. *Reproduction in Domestic Animals* published by Wiley-VCH GmbH.

KEYWORDS

infection, inflammation, postmating, postpartum, prophylaxis, uterus

1 | INTRODUCTION

The reproductive tract of the female is colonized by varying numbers of commensal organisms. These may be helpful for controlling pathogenic organisms by competing with them and possibly by priming the immune systems against pathogens. The commensals themselves may cause disease if situations arise that allow them to persist or penetrate tissues. Generally, there is a larger number of organisms present on the perineum and vulva and fewer present at the cervix and within the uterus. The vulval lips, vestibule-vaginal junction and the cervix form the three principal barriers to the introduction of bacteria. After parturition, however, these anatomical barriers are disrupted, and the reproductive tract compartmentalization is temporarily lost. Interestingly, in some domestic species, a shift in the number or type of organisms may also be linked to mating (or deposition of seminal plasma directly into the uterus), poor or inadequate conformation of the vulva or iatrogenic events (England et al., 2021, O'Leary et al., 2004; Palm et al., 2008; Recuero et al., 2020).

Uterine inflammation associated with parturition is a physiologically relevant event in all domestic animal species. Postpartum uterine inflammation should trigger robust taxis and function of immune cells (notably phagocytic cells such as polymorphonuclear leukocytes [PMN] and macrophages) to control the potential overgrowth of pathogenic bacteria and prevent uterine dysbiosis (Gilbert & Santos, 2016; Pascottini & LeBlanc, 2020). Subsequent uterine debris elimination in the form of a discharge from the uterus, modulation of inflammation and endometrial tissue remodelling is necessary to accomplish uterine involution (Kolaczowska & Kubes, 2013). Poor hygiene, prolonged or traumatic parturition, obstetrical intervention and retained placenta may all increase the risk of uterine contamination. Endometritis that occurs after parturition may persist for some time, either as a low-grade disease that often manifests as vaginal discharge without systemic illness (in some species termed clinical endometritis) or may remain subclinical where features are only detected by sampling the uterus.

In several species, the contamination of the uterus at the time of mating is prevented by the presence of a significant cap of mucus that covers the cervix and forms a barrier to introduced organisms but does allow the entrance of motile sperm. In other species, notably the horse, pig and dog, there is no significant cervical barrier, and a relatively large volume of ejaculate is deposited into the uterus. The normal mechanism for restoring the uterine microbiome includes uterine contractions and the female's immune response; effectively there is a short-term physiological endometritis following each mating. In certain circumstances where drainage of the introduced microorganisms and ejaculatory fluid is impaired or the immune response is inadequate, the uterine microbiome remains disturbed, resulting in a persistent breeding-induced endometritis (PBIE). It is

also possible at least in the mare and bitch that microorganisms may enter the uterus during oestrus without the need for breeding; this may be a significant problem in the mare with poor perineal conformation. This condition may perhaps be best described as a post-oestrous endometritis.

When writing a review providing information on endometritis in the four important domestic animal species—cattle, horse, pig and dog—it becomes apparent that research that has been undertaken on this topic varies considerably among the species regarding the number of studies that have been published over the years. When searching Scopus for the keyword combinations endometritis and cattle, endometritis and horse, endometritis and pig or endometritis and dog for the years 2014 to 2023, there were 766, 190, 51 and 48 hits, respectively. Although endometritis is considered among the most important reasons for sub- and infertility irrespective of species, the need and opportunity to investigate the condition clearly vary considerably. This depends on the economic impact, the value of the individual animal and the importance of achieving pregnancy, as well as the approaches available to assess the genital tract for in-depth diagnosis (for example uterine sampling is difficult in the bitch and sow). The objective of this article is to review general and comparative aspects of the diagnosis and classification, pathogenesis, preventive strategies and therapeutics of endometritis in domestic species with a specific focus on cows, mares, sows and bitches.

2 | IMPORTANCE AND CLASSIFICATION

Endometritis has been described to be one of the leading causes of infertility in cows, mares, sows and bitches (England et al., 2021; Grahofer et al., 2020; Morris et al., 2020; Pascottini & LeBlanc, 2020). It interferes with fertility by creating suboptimal conditions for sperm transportation and storage, oocyte maturation and ovulation, zygote development, implantation, as well as embryonic and foetal growth (Gilbert, 2011). The term 'endometritis' is often misused and indistinctively referred in veterinary practice as 'endometrosis', 'endometriosis' or 'metritis'. From the histopathological point of view, endometritis is the superficial inflammation of the endometrium that encompasses disruption of luminal epithelium, vascular congestion, oedema and infiltration with inflammatory cells (active inflammation), no deeper than the *stratum spongiosum* (Figure 1; Bondurant, 1999). Endometrosis connotes a wide range of chronic, often degenerative changes characterized by fibrosis and cystic dilatation of endometrial glands (Allen, 1993). Endometriosis is the extra-uterine implantation of endometrial tissue (Bulun, 2009), a condition which largely occurs in primates. Metritis, on the other hand, is a more severe condition where all the layers of the uterus namely the endometrium, lamina muscularis and serosa are inflamed

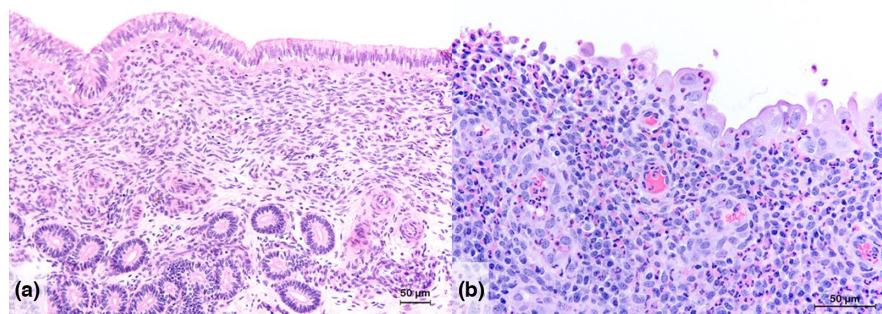


FIGURE 1 Holstein cow endometrial biopsies collected in the fifth week postpartum, stained with haematoxylin and eosin and evaluated by light microscopy. (a) Healthy endometrium with intact columnar epithelium. Endometrial glands can be seen in the lower third section of the image, this section is known as the *stratum spongiosum*. The section located between the epithelium and the *stratum spongiosum* is denominated as *stratum compactum* as no endometrial glands are present there ($\times 200$ magnification). (b) Superficial endometrial inflammation (endometritis) that encompasses disruption of luminal epithelium, vascular congestion, oedema and infiltration with inflammatory cells, mostly PMN ($\times 400$ magnification). Scale bar = 50 μm .

(Sheldon et al., 2006). In the following section, we will elaborate on the importance and classification of endometritis in cows, mares, sows and bitches.

2.1 | Cow endometritis: Importance and classification

Uterine involution and mechanisms leading to uterine disease (and infertility) are essentially different between dairy and beef cows. Overall, there is limited peer-reviewed literature on beef cattle endometritis, and the available information is often conflicting (Machado Pfeifer et al., 2018; Ricci et al., 2015; Ricci et al., 2017; Santos et al., 2009). This is because diagnostic criteria established by dairy research are simply extrapolated to beef cows. This is inaccurate, since environmental, genetic, managerial and physiological differences exist between beef and dairy cows and even among different cattle breeds (Sartori et al., 2016). Therefore, this section will elaborate on dairy cow endometritis research only.

One out of two intensively managed, high-producing dairy cows will develop reproductive tract infection and inflammatory disease within 6 weeks after calving (LeBlanc, 2014). Red-brown and watery or purulent and viscous foetid vulvar discharge (with or without fever) within 3 weeks after calving is defined as metritis and occurs in 10%–20% of dairy cows (Sheldon et al., 2006). Between 4 and 6 weeks after calving, approximately 30% of dairy cows may have signs of delayed uterine involution, characterized by the presence of a uterine exudate found within the vagina (Sheldon et al., 2006). If the origin of this exudate remains unknown, the condition is referred to as purulent vaginal discharge (PVD) (Dubuc et al., 2010a). Remarkably, half of PVD cases occur without endometrial inflammation (vaginitis, cervicitis or both combined) (Deguillaume et al., 2012; Dubuc et al., 2010a). Thus, the current classification of reproductive tract inflammatory disease in dairy cows is as follows: vaginal exudate without endometrial inflammation (diagnosed via endometrial cytology) is referred to as PVD. Purulent vaginal discharge

accompanied by endometrial inflammation is clinical endometritis (CE). Cows that do not show signs of PVD are, however, not necessarily healthy because 10%–40% of ‘apparently healthy’ dairy cows may have subclinical endometrial inflammation (diagnosed via cytology) (Wagener et al., 2017). This condition is referred to as subclinical endometritis (SCE) or cytological endometritis.

Dairy cattle operations aim to have cows pregnant at a biologically optimal and economically profitable time after parturition. Plentiful data have documented that dairy cows with endometritis have a reduced probability of pregnancy at first insemination, greater pregnancy losses or reduced pregnancy rate through lactation (Denis-Robichaud & Dubuc, 2015a, 2015b; Dubuc et al., 2010a; Bogado Pascottini et al., 2017). Taking it all together, the detrimental effect of endometritis on time to pregnancy is somehow similar among studies and is reported to be approximately 30 days (affected cows need on average 30 days longer to become pregnant than unaffected cows) (Dubuc et al., 2010a; LeBlanc et al., 2002). Importantly, endometritis causes no direct loss of milk production or mortality. Although the impact of endometritis on culling is not well studied, recent preliminary data showed that poorer reproductive performance associated with SCE may be linked with a greater culling risk (Valdmann et al., 2022).

2.2 | Mare endometritis: Importance and classification

Endometritis in the mare can be divided into acute infectious, chronic infectious or post-mating-induced endometritis. Endometritis that is not associated with parturition or the postpartum period compromises exclusively the endometrium and no other parts of the uterine wall. It therefore occurs without systemic effects. In most cases, infectious endometritis develops from endometrial infection as a cause of PBIE. Infection of the endometrium, however, can also occur in mares that have never been bred, but where anatomical defects together with impaired

uterine clearance allow bacteria to enter the uterus and contaminate the endometrium. Endometritis is considered a major cause of infertility in horses affecting 25%–60% of barren mares (Traub-Dargatz et al., 1991) and contributing considerably to economic loss. Uterine infection is the reason for conception failure, early pregnancy loss, abortion due to bacterial placentitis, birth of septic foals and postpartum metritis.

Postpartum inflammation of the uterus in mares does not only compromise the endometrium but the whole uterine wall often including the perimetrium. This condition is therefore referred to as metritis. It is often considered a life-threatening condition because it is associated with septicemia and endotoxemia and may be followed by complications such as laminitis (Frazer, 2003). Postpartum metritis in mares occurs within 7–10 days after delivery and has normally a low incidence. This, however, increases in cases with dystocia and/or retained placenta. Immediate recognition and treatment cannot only prevent complications and sequelae but also rapidly restore fertility.

2.3 | Sow endometritis: Importance and classification

Uterine disorders, especially endometritis, lead to reproductive failure in sow herds. This pathological state can occur after farrowing and during the puerperium but also following artificial insemination or natural mating. The within-herd prevalence of endometritis varies between 1.4% and 60% (Biksi et al., 2002; Heinonen et al., 1998; Kauffold et al., 2005a, 2005b; Monteiro et al., 2022) and commonly a chronic form of uterine inflammation occurs in sows (Kauffold et al., 2005a, 2005b). Endometritis is one of the main reasons for the culling of a breeding sow (Heinonen et al., 1998). The condition has a major impact on the economic output of a farm, due to reduced reproductive performance (Koketsu et al., 2017), but also decreases the health and welfare of sows and their offspring (Björkman & Grahofer, 2020; Grahofer et al., 2020).

The clinical diagnosis of endometritis in sows is challenging. Until now, no consistent clinical or histopathological nomenclature for endometritis in breeding sows is available (Grahofer et al., 2020). The classification of endometritis is largely dependent upon the time point of occurrence in the reproductive cycle, and this seems to be an appropriate way that helps to evaluate risk factors and to define preventive measures on sow farms. Hence, a classification in puerperal and nonpuerperal endometritis is often used (Kauffold & Wehrend, 2014). In addition, endometritis can be categorized depending on the clinical signs into subclinical vs. acute, subacute and chronic occurrence (De Winter et al., 1994; Muirhead, 1986). The severity of endometritis can be evaluated histologically according to the percentage of tissue containing inflammatory cell infiltrate (Kauffold et al., 2005a, 2005b). For the interpretation of histology, the stage of the oestrous cycle should be considered to avoid misinterpretation (Dalin et al., 2004).

2.4 | Bitch endometritis: Importance and classification

In the bitch, it was recognized in the 1950s that acute endometritis was most commonly identified in the early part of the luteal phase (Dow, 1959), and although this was likely a mating-induced or postoestrous endometritis, that was not recognized at the time. The relationship between endometritis and infertility has only recently been demonstrated (Fontaine et al., 2009; García Mitacek et al., 2017; Gifford et al., 2014; Mir et al., 2013). Most recently, England et al. (2021) provided a commentary on the likely aetiology of postmating and postoestrous endometritis in the bitch and some suggestions on the possibility of persistence of chronic endometritis. The lack of detailed work makes it difficult to ascertain the importance of the disease as a cause of infertility and the suggested classifications of (1) mating-induced, (2) postestrus and (3) chronic endometritis are yet to be fully debated. Most cases of postpartum infection involve the whole of the uterine wall and the condition is therefore referred to as metritis. This condition is usually associated with significant clinical disease related to septicaemia. Fortunately, it has a low incidence but may occur following prolonged parturition, dystocia, retained foetal membranes or also likely where there is an unhygienic whelping environment. Information on the persistence of postpartum infection beyond the acute metritis phase is lacking.

2.5 | Importance and classification: Comparative aspects

All domestic species reviewed here experience some degree of postpartum or puerperal endometritis that may perdure after the normal time of uterine involution to chronic or pathological endometritis (Table 1). The typical clinical sign for this type of 'clinical' endometritis is the presence of purulent vaginal exudates. The origin of this purulent material, however, often remains undiagnosed. In cows, endometritis may occur without clinical signs (not visible with the naked eye) and therefore it is named SCE. Subclinical endometritis has been described in the mare, but it has not yet been described in sows and bitches. This is because, in the latter two species, it is more challenging to collect endometrial specimens due to difficulties in accessing the uterine lumen. The occurrence of SCE in sows and bitches cannot be discarded. In the horse, pig and dog where ejaculation occurs effectively directly into the uterus, PBIE may occur. In natural mating, the deposition of semen into the fornix of the cow may trigger mild inflammation, but because of the small volume of the bull ejaculate (typically 4–8 mL) and lack of direct contact of seminal fluids with the endometrium, bovine postmating endometritis is not a relevant clinical condition. In this context, it is interesting to note that sperm can induce changes in the endometrial gene expression profile of the cow, but these changes are only modest (Recuero et al., 2020). Despite the extensive use of artificial insemination in dairy cattle, the low sperm concentration (10×10^6

TABLE 1 Comparative aspects of endometritis in domestic animal species.

	Cow	Mare	Sow	Bitch
Prevalence	CE and PVD: 20–30% SCE: 9–76% but most commonly between 25 and 35%	60% in barren mares	1–60% differing within herds	Mating-induced endometritis largely relates to age changes, with up to 40% of older bitches having endometrial hyperplasia
Time point	Postpartum	Postpartum but most frequently after breeding	Postpartum and postbreeding	Postbreeding and postpartum
Clinical sign	PVD: Presence of purulent (at the fourth week postpartum) or mucopurulent (from the fifth week postpartum) discharge in the vagina SCE: >5% PMN between the fourth and fifth week postpartum CE: PVD + SCE	Discharge from the vulva, cervical discharge (speculum examination) and uterine fluid accumulation (transrectal ultrasound examination)	Most often subclinical, unspecific clinical signs such as vaginal discharge, fever, reduced feed intake	Postbreeding there is delayed uterine fluid clearance and there may be a postmating vaginal discharge
Diagnosis	PVD: vaginoscopy, gloved hand or metricheck. SCE: endometrial cytology (cytobrush, low-volume lavage or cytotope)	Gynaecological examination including bacterial culture and cytology	Analysis of reproductive performance characteristics, ultrasound examination, Evaluation of urogenital tract at culled sows, Bacteriological investigation	Persistence of uterine fluid detected with ultrasound, increased PMNs on endometrial sampling
Life threatening	No	Postpartum: yes Otherwise: no	No	No

Abbreviations: CE, clinical endometritis; PVD, purulent vaginal discharge; SCE, subclinical endometritis.

to 30×10^6) used and the small volume (0.25–0.5 mL) of a frozen-thawed semen straw results in PBIE being insignificant following insemination.

3 | DIAGNOSIS

Due to the complexity of uterine involution and the thin line between physiological and pathological inflammation, it is challenging to establish solid diagnostic criteria for endometritis. In cows, horses and sometimes in pigs, cut-off values are established based on the detrimental impact of an indicative sign of endometritis on subsequent reproduction. The most used sign to diagnose endometritis is the evaluation of the nature (e.g. colour, consistency, odour and location) and duration of vaginal discharge postpartum or postmating. Postpartum, the origin of vaginal discharge may be associated with endometritis, cervicitis, vaginitis, cystitis or any of those combined (described in cows and sows). Postmating, the volume of uterine exudate is generally low, and it often goes unnoticed in sows and

dogs, but in mares, PBIE can produce large amounts of free intrauterine fluid easily visualized via ultrasonography. Similarly, uterine fluid may be detected with ultrasound in sows and dogs, and in the latter species, endometrial hyperplasia may be distinguished by the presence of small cysts; this condition may predispose to postmating endometritis. Thus, accurate diagnostic methods should be implemented to precisely determine the origin and nature of vaginal discharges. In cattle and horses, the diagnostic criteria are well established and complementary techniques such as ultrasound, cytology, histopathology and bacteriology are often implemented. In sows and bitches, histopathology has been described, but the literature is scant.

3.1 | Cow endometritis: Diagnosis

Uterine disorders are one of the most studied conditions in dairy cows in the last 20 years; plentiful information on this topic can thus be found in current literature. The overall quality of reporting of

definitions, validation and diagnostic methods is, however, inconsistent and generally low (de Boer et al., 2014). For the present review only well-designed, large-scale epidemiological studies were considered for the basis of PVD, CE and SCE definitions (Denis-Robichaud & Dubuc, 2015a, 2015b; Dubuc et al., 2010a; Pascottini et al., 2017).

Transrectal palpation of the genital tract is a common approach to evaluate for an enlarged uterus with fluctuating content or an indurated uterine wall (Callahan & Horstman, 1993). This practice is, however, subjective and its diagnostic outcome has no or little association with reproductive performance (Sheldon et al., 2006). Still, a cervical diameter of >7.5 cm in the fourth week postpartum has predictive value for infertility (LeBlanc et al., 2002), but cervicitis may not be primarily associated with endometritis. Most field veterinarians use transrectal ultrasound for routine clinical examination of the reproductive tract of dairy cows. Transrectal uterine ultrasonographic evaluation can distinguish the diameter of the uterine content (0 to ≤2 cm, >2 to ≤5 cm or >5 cm) and its echogenicity (anechoic, mixed echogenicity or hyperechoic). In this regard, field studies demonstrated that the presence of fluid (>2 cm with mixed echogenicity or worse) in the uterine lumen between 4 and 6 weeks postpartum has a significant effect on the reduction in the relative pregnancy rate in comparison with cows that appeared 'clean' at examination (Kelly et al., 2020; Šavc et al., 2016). The measurement of the endometrial thickness as indicative of endometritis has also been proposed (Barlund et al., 2008). Yet, endometrial thickness is dependent on the oestrous cycle stage (follicular or luteal phase) and no standardization has been done to validate this procedure (Barlund et al., 2008). In general, transrectal ultrasound is a fair technique to detect the presence of purulent material in the uterine lumen. However, we hypothesize that the diagnostic accuracy can be influenced by the size and position of the cow and the location of the probe on the uterine horn, the stage of the oestrous cycle and the experience and skills of the operator. For a greater diagnostic accuracy, a combination of ultrasound, vaginal mucus scoring and endometrial cytology has a higher predicting capacity than either method used alone (Barlund et al., 2008; Denis-Robichaud & Dubuc, 2015a, 2015b; Šavc et al., 2016).

The gold standard to diagnose PVD is the visual evaluation of vaginal exudates (Sheldon et al., 2006). Although useful this evaluation is not always reliable because purulent secretions may remain in the uterine lumen or the vaginal floor and require careful examination to detect. Purulent vaginal discharge diagnosis should be performed by vaginoscopy, a gloved hand or the metrichheck device (McDougall et al., 2007; Pleticha et al., 2009). Although a slightly higher proportion of cows are diagnosed PVD-positive when using the metrichheck device (Pleticha et al., 2009), the use of any of these 3 techniques provides similar outcomes (Pleticha et al., 2009). Thus, the choice of diagnostic approach for PVD is merely based on practical aspects, such as ease of use and hygiene. The visual evaluation of vaginal discharge is standardized and classified in a 0 to 3 score (Williams et al., 2005). A score 0 is the absence of or clear mucus, a score 1 is mucus containing flecks of pus, a score 2 is discharge containing less than 50% of pus (mucopurulent material) and a score of 3 is discharge composed of more than 50% of pus (purulent material)

or sanguineous material. The cut-off for PVD at the fourth week postpartum is score 3 (purulent discharge) and from the fifth week postpartum on is score 2 (mucopurulent discharge). For both cases, cut-off points were developed based on worse reproductive performance when compared to healthier scores (Dubuc et al., 2010a; LeBlanc et al., 2002).

Subclinical endometritis is the superficial inflammation of the endometrium (no deeper than the *stratum compactum*), evidenced by a relative increase in the number of PMN in the uterine lumen (relative to endometrial epithelial cells) (Kasimanickam et al., 2004). Subclinical endometritis is not visible by the naked eye, hence complementary examinations are necessary for its diagnosis. Histopathology, ultrasound and cytology (and its surrogate tests) are described as available methods for the diagnosis of SCE (Kasimanickam et al., 2004; Meira Jr et al., 2012; Pascottini et al., 2016a). Histopathology allows for the direct evaluation of acute and chronic changes within the endometrium (Figure 1), but biopsy sampling is invasive and potentially harmful to fertility, its processing and evaluation are technically complex, and its predictive value for fertility is inexistent (Bonnett et al., 1991; Chapwanya et al., 2009; Pascottini et al., 2016b). On the other hand, by using ultrasonography, the presence of small amounts of fluid in the uterus between 4 and 6 weeks in the absence of clinical signs is associated with a significant reduction in pregnancy risk when compared to 'clean' cows (Gobikrushanth et al., 2016; Kasimanickam et al., 2004; López-Helguera et al., 2012). Ultrasonography has, however, a lower predictive value for fertility when compared to endometrial cytology (Kasimanickam et al., 2004). Although ultrasonography is an easy and rapid technique to implement in practice, it is not accurate enough to diagnose SCE when it is not accompanied by endometrial cytology.

Transcervical endometrial cytology is the most popular method for the diagnosis of SCE and its diagnostic potential has been validated in numerous large-scale studies (Denis-Robichaud & Dubuc, 2015a, 2015b; Dubuc et al., 2010a, 2010b; Pascottini et al., 2017). Endometrial cytology samples can be collected using the cytobrush or low-volume lavage techniques in the postpartum period (Gilbert et al., 2005; Kasimanickam et al., 2004). The cytotope technique allows for endometrial cell collection at the time of artificial insemination (Pascottini et al., 2015). Endometrial sampling using cytobrush or low-volume lavage yields similar outcomes, but cytobrush sampling is easier, provides results faster (no centrifugation is needed), and the quality of the slides is better (less distorted cells) in comparison with low-volume lavage (Pascottini et al., 2016a; Van Schyndel et al., 2018). Cytotope sampling is as easy as performing artificial insemination (Pascottini et al., 2017). Subclinical endometritis is typically characterized by >5% PMN to epithelial cells in cytobrush or low-volume lavage samples collected between 4 and 6 weeks postpartum (Figure 2; Wagener et al., 2017). If samples are collected at insemination using the cytotope, a ≥1% PMN to epithelial cells cut-off should be implemented (Bogado Pascottini et al., 2017). The above-mentioned cut points were developed based on worse reproductive performance when compared to lower PMN percentage scores in large-scale epidemiological studies. Although endometrial cytology provides consistent results, it is not a cow-side

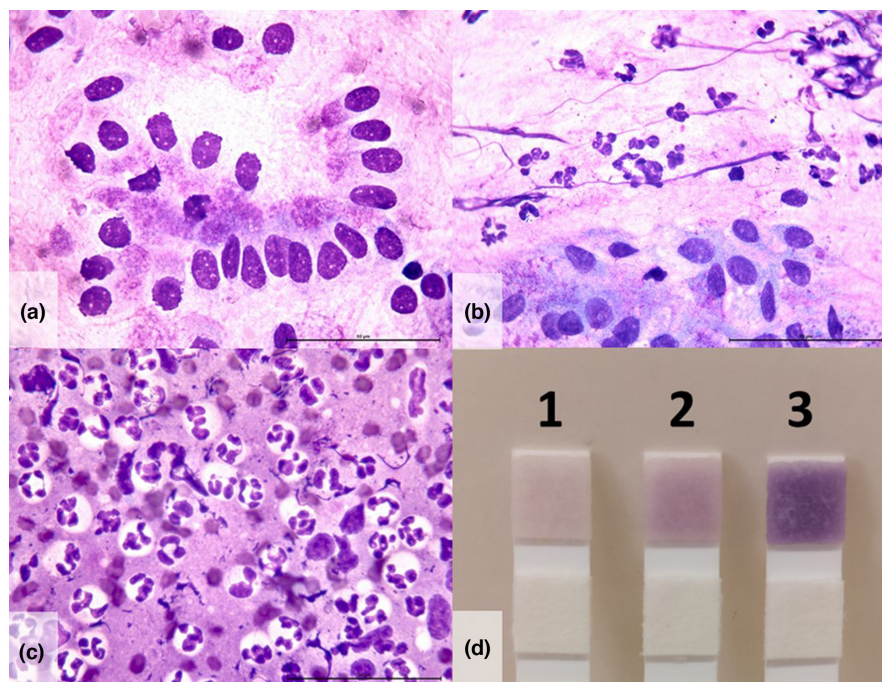


FIGURE 2 (a–c) Holstein cow endometrial cytology smears collected in the fifth week postpartum using the cytobrush technique, stained with Wright Giemsa and evaluated by light microscopy ($\times 400$ magnification; scale bar = $50\ \mu\text{m}$). (a) Healthy endometrial cytology sample, only endometrial epithelial cells are visualized. (b) Presence of endometrial epithelial cells and polymorphonuclear leukocytes, indicative of subclinical endometritis. (c) High amounts of polymorphonuclear leukocytes with some fragmented epithelial cells and erythrocyte contamination, indicative of clinical endometritis. (d) Leukocyte esterase is a surrogate test for subclinical endometritis. Colour intensity represents the proportion of polymorphonuclear leukocytes in an endometrial sample and is classified as 0 = none or trace number of leukocytes (image not shown), 1 = small number of leukocytes, 2 = moderate number of leukocytes and 3 = large number of leukocytes.

test. Leukocyte esterase is a surrogate test, and it has been validated on cytobrush and low-volume lavage samples providing reasonable accuracy without the necessity of slide staining and microscopic evaluation (Figure 2; Van Schyndel et al., 2018). Furthermore, to date, there is not a truly cow-side test for SCE (e.g. blood or milk biomarker) because endometrial sampling requires passage through the cervix, which involves time and skills to collect a sample.

3.2 | Mare endometritis: Diagnosis

The reproductive stage and history of the mare require consideration with a specific focus on her age, parity, reproductive status, foaling history, history of previous uterine infection or associated treatments. Clinical signs of endometritis in horses include discharge from the vulva, cervical discharge (speculum examination) and free uterine fluid accumulation (transrectal ultrasound examination). The clinical findings should be supported by laboratory-based examinations including endometrial cytology and bacterial culture that allows for the identification of bacteria involved and their antimicrobial sensitivity (Scott et al., 2022). Depending on the case, endometrial histology (biopsy) or hysteroscopy should be considered. Because endometritis in horses is exclusively a localized problem, blood parameters are not of diagnostic value (Katila, 2016).

Endometrial cytology may help to identify SCE (e.g. Riddle et al., 2007). Cytology results may be biased by the bacteria involved,

as for example, *E. coli* infections can suppress the PMN response, or latent infection with so-called dormant *Streptococci* spp. is not associated with an increased number of PMN in cytology slides (Christoffersen et al., 2015a; Christoffersen et al., 2015b; LeBlanc et al., 2010; Petersen et al., 2015).

Whereas the collection of endometrial swabs is the most frequent approach for bacterial culture, culture of cytobrush samples, endometrial biopsies or (low) volume uterine lavage fluid increases the sensitivity and specificity of bacterial isolates (Christoffersen et al., 2015a; Christoffersen et al., 2015b; Katila, 2016; Ravaioli et al., 2022). The cytotype provides sample smears of greater quality and less blood contamination than the cytobrush (Ibrahim et al., 2021). A leucocyte-esterase reagent strip that was developed as a stall-side test for the diagnosis of endometritis in mares, however, proved useful to diagnose endometritis in severe cases but was not sensitive enough to rule out endometritis (Kelley et al., 2019).

3.3 | Sow endometritis: Diagnosis

Sows with endometritis might be presented with various unspecific clinical symptoms including decreased feed intake, fever, vulvar discharge, anestrus or irregular oestrus and infertility (Wang et al., 2020). However, endometritis in sows is often subclinical (Kauffold et al., 2005a, 2005b). Therefore, a complementary diagnostic procedure is needed. In this regard, analyses of the

reproductive performance characteristics can help to identify affected animals and perform further diagnostics.

Sows with impaired fertility associated with vaginal discharge are more likely to have bacterial infections compared to sows with chronic endometritis (De Winter et al., 1995). Furthermore, vaginal discharge more than 6 days after farrowing is indicative of puerperal endometritis but vaginitis, cystitis and pyelonephritis should be ruled out (Waller et al., 2002). A cervical swab in sows with vaginal discharge for bacteriological investigation can be taken, but the results can be misleading due to contamination. Intrauterine fluid and retained foetal and placental parts can be used as an indicator for endometritis by ultrasonography (Björkman et al., 2018; Grahofer et al., 2020, 2022; Kauffold et al., 2005a, 2005b; Monteiro et al., 2022). Postmortem examination of genital organs from slaughtered sows with reproductive failure is a valuable diagnostic tool to identify reproductive disorders on farms (Dalin et al., 1997). For reliable interpretation of endometrial histology, information about the time point of the reproductive cycle is important (Dalin et al., 2004). Bacteriological investigation from uteri after slaughter provides better results because contamination during the sampling procedure is less likely (Sipos et al., 2014). In a recent study, where 24 uteri with macroscopical signs of endometritis were sampled for bacteriological investigation, 45.8% of the samples yielded mixed infections with *E. coli* (Monteiro et al., 2022).

3.4 | Bitch endometritis: Diagnosis

Bitches with mating-induced endometritis seem largely to present with a reduced chance of pregnancy or a small litter size (England, Burgess et al., 2012; Fontaine et al., 2009; Mir et al., 2013). Although only a small number of studies have been described and they involve few bitches, the observations are quite interesting. For example, Mir et al. (2013) found that of 14 bitches that were recently mated but did not get pregnant, four (28%) had endometritis diagnosed histologically.

A proportion of bitches that develop mating-induced endometritis also have a concomitant endometrial hyperplasia (Gifford et al., 2014), which can be diagnosed using an ultrasound examination of the uterus (Moxon et al., 2016). In these cases, indirect diagnosis of endometritis may also be made by ultrasound detection of delayed fluid clearance after mating and in more detailed studies by detection of decreased uterine contractions and increased accumulation of PMNs following transcervical sampling from the uterus (England, Burgess et al., 2012; England, Moxon et al., 2012). Precise diagnosis of mating-induced and postoestrous endometritis requires uterine biopsy (Gifford et al., 2014; Mir et al., 2013). Cases of chronic endometritis which persists through the luteal phase and anoestrus to the next oestrous cycle may be diagnosed by the persistence of uterine luminal fluid detected with ultrasound (Lyman et al., 2018). The author has also identified a number of cases of chronic endometritis using ultrasounds following postwhelping metritis; presumable a persistence of postpartum infection similar to that seen in other species (GE, unpublished observations).

3.5 | Diagnosis: Comparative aspects

Due to the shorter time required to complete uterine involution in the mare and sow in comparison with the cow and bitch, the physiological discharge after parturition and intrauterine fluid accumulation varies among species and must be considered in the diagnosis of endometritis. In all species, persistency of fluid in the uterine lumen, which can be diagnosed using ultrasonography, is a valid indicator for endometritis. Further diagnostic procedures vary considerably among cows, mares and bitches in comparison with sows, due to the economic impact and the value of the individual animals. Endometrial cytological examinations are routinely conducted in cows and mares but are difficult in the bitch and performed only in a few clinics. Endometrial biopsy is a popular diagnostic tool in mares but is only occasionally used in cows and bitches. In sows, in vivo, endometrial cytology or biopsy have not been described. Again, this is merely based on economic reasons, because sows that are not timely pregnant after farrowing are rapidly remitted to the slaughterhouse. In this species, postmortem examinations of the urogenital tract of 'problem' sows will be conducted to get a herd-level diagnosis.

4 | PATHOGENESIS

Genesis of puerperal and mating-induced endometritis lies within the balance of three key components: immune function, uterine microbiota and metabolic stress. Robust innate immune function is essential to timely clear bacteria and inflammatory products but without harming the endometrium. This should be accompanied by adequate myometrial contractions, to eject postpartum and postmating debris. A balanced uterine microbiota is essential to impede the overgrowth of potentially pathogenic bacteria and thus infection. Adequate heat detection and hygienic insemination techniques are also indispensable to avoid the introduction of contaminants or pathogenic bacteria into the uterine cavity (Table 2). In dairy cows, the commencement of lactation and in consequence, metabolic stress weakens the immune function and therefore is key for the pathogenesis of endometritis. In sows, the metabolic challenge begins already in late gestation due to high energetic demands for the growth of the large litters and continues in the early stage of lactation, leading to an improper function of the immune system and therefore increase the prevalence of endometritis in our hyperprolific sows (Oliviero et al., 2019; Peltoniemi et al., 2021).

4.1 | Cow endometritis: Pathogenesis

Artificial insemination that resulted in nonpregnancy can trigger SCE in nulliparous heifers, probably due to the introduction of contaminants into the uterine lumen (Pascottini et al., 2016). Though, apart from that unique finding, endometritis almost exclusively happens in the postpartum period of dairy cows. After calving, the endometrium and the birth canal of dairy cows are commonly traumatized, and it

TABLE 2 Comparative aspects of bacteria involved in endometritis in domestic animal species (+++ great importance and frequently isolated, ++ moderate involvement, + and (+) rare involvement).

Bacteria	Cow	Mare	Sow	Bitch
<i>Escherichia coli</i>	+	+++	+++	++
<i>Streptococcus</i> sp.	+	+++	+++	++
<i>Staphylococcus</i> sp.	++	++	++	++
<i>Trueperella</i> sp.	+++	–	++	–
<i>Proteus</i> sp.	+	+	+	–
<i>Klebsiella</i> sp.	+	+	++	–
<i>Corynebacterium</i> spp	+	(+)	+	(+)
<i>Pseudomonas</i> spp.	+	+	+	–
<i>Chlamydia</i> spp.	+	+	+	–

will largely depend on the robustness of the immune system to maintain eubiosis within the uterine cavity (Pascottini & LeBlanc, 2020; Sheldon et al., 2019). Although potentially pathogenic bacteria are commonly present in the genital tract of healthy cows (Galvão et al., 2019), they are maintained at relatively low numbers by adequate modulation of inflammation, and probably by signalling molecules of 'beneficial bacteria' within the same ecosystem (Pascottini & LeBlanc, 2020). Nevertheless, maladaptation to metabolic stress driven by the high milk production (notably high circulating fatty acids and β -hydroxybutyrate) in the postpartum period of dairy cows weakens the innate immune function, and consequently, uterine diseases may occur (Pascottini et al., 2022). Thus, current evidence indicates that the genesis of uterine diseases in postpartum dairy cows lies in the unbalance of the following trifecta: immune function, shifts in the microbiota and metabolic stress. The role of viruses and other microorganisms is less explored, although the co-action of bovine herpesvirus 4 and *Histophilus somni* has been suggested to play a role in the pathogenesis of PVD (Szenci et al., 2016).

Culture-dependent, as well as culture-independent (16S rRNA gene and shotgun metagenomics sequencing) methods, found causalities between pathogenic bacteria and CE (and PVD) (Galvão et al., 2019). In other words, uterine microbiota dysbiosis with increased abundances of *Bacteroides*, *Ureaplasma*, *Helcococcus*, *Fusobacterium*, *Trueperella* and/or *Porphyromonas* are responsible for the purulent uterine discharges seen in cows with CE (and PVD). Notably, *Trueperella pyogenes* is the most commonly recovered bacteria in uterine samples collected and cultured from cows with CE (and PVD) (Carneiro et al., 2016; Gilbert & Santos, 2016; Williams et al., 2005) and often appears in greater relative abundance (compared with healthy uteri) in culture-independent based studies (Machado et al., 2012; Miranda-CasoLuengo et al., 2019; Pascottini et al., 2020). Conversely, SCE has not been associated with bacterial dysbiosis (Pascottini et al., 2020; Wang et al., 2018). Current data support the hypothesis that SCE is the result of maladaptation to negative energy balance and dysregulation of inflammation rather than uterine infection (Pascottini & LeBlanc, 2020; Wagener et al., 2017). Briefly, excessive negative energy balance and systemic

inflammation in the second week postpartum characterized by high circulating nonesterified fatty acids, β -hydroxybutyrate and haptoglobin are the main risk factors for SCE (Cheong et al., 2011; Dubuc et al., 2010b). Circulating PMNs exposed to this 'unhealthy' environment becomes dysfunctional when reaching the postpartum uterus (Lietaer et al., 2022). By neutrophil dysfunctionality, we refer to altered function capacities such as oversensitivity to degranulate and form extracellular traps, which have secondarily harmful effects on surrounding tissues, and insufficient phagocytic capacity. Moreover, dysfunctional PMN are unable to undergo apoptosis and abandon the genital tract to accomplish uterine clearance (Lietaer et al., 2023). This dysregulation of the innate immune function is believed to cause aseptic persistent inflammation of the endometrium also known as SCE.

4.2 | Mare endometritis: Pathogenesis

In mares after mating or insemination, there will be an inflammation of the endometrium, which typically ceases within 24–36 h (Christoffersen et al., 2012; Fedorka et al., 2018; Katila, 1995; Watson et al., 2001). This inflammation is characterized by free fluid in the uterine lumen and an influx of PMNs. If a mare fails to clear the uterine lumen from the physiological inflammatory response within 36–48 h, the condition is referred to as PBIE. This makes the mare susceptible to a secondary endometrial infection (Pycoc & Allen, 1990). By contrast, a mare capable of removing all the inflammatory associated uterine contents within 24–36 h after mating is usually resistant to such infection and will have her uterine environment prepared for the arrival of a conceptus at approximately 6 days after ovulation.

Myometrial contractions together with an adequate innate immune response at the endometrial level are responsible for eliminating excess spermatozoa and cells, bacteria and inflammatory debris from the uterine lumen. During the first 24 h after the breeding of a mare, there is a rapid increase in the pro-inflammatory cytokines, interleukin (IL)-1 β , IL-8 and interferon- γ , as well as activation of PMNs (Christoffersen et al., 2012). The PMNs release lytic enzymes and phagocyte bacteria. The timely cessation of the inflammatory response to mating requires a balance between both pro- and anti-inflammatory factors (Marth et al., 2018; Woodward & Troedsson, 2015), whereas in susceptible mares, endometrial expression of pro-inflammatory cytokines is inadequate and prolonged, the abundance of mRNA expression for the anti-inflammatory cytokines is reduced but that of pro-inflammatory cytokines increased. This imbalance is associated with increased numbers of PMNs in the uterine lumen (Christoffersen et al., 2012; Christoffersen & Troedsson, 2017; Woodward et al., 2013).

In mares, the uterine mechanical clearance mainly depends on myometrial contractions that are induced and maintained by oxytocin and further stimulated by prostaglandin- $F_{2\alpha}$ produced by PMNs (Troedsson, 1999). Myometrial contractions remove uterine contents through the relaxed cervix into the vagina (Campbell &

England, 2004; Risco et al., 2009). Intrauterine fluid is, however, also removed by lymphatic drainage (LeBlanc et al., 1995). Anatomical defects of the female genital tract (e.g. poor perineal conformation, vaginal stretching, incomplete cervical opening, a pendulous uterus or myometrial and endometrial degeneration) are detrimental to uterine clearance. It has been assumed that repeated foaling but also increasing age in mares that never foaled contribute to the development of such defects (Evans et al., 1987; LeBlanc et al., 1989). In addition, myoelectrical activity may be impaired especially in aged mares (Rigby et al., 2001) and is further reduced by intrauterine accumulation of nitric oxide in susceptible mares (Alghamdi et al., 2005; Khan et al., 2017).

In mares with PBIE, prolonged inflammation challenged by pathogenic bacteria may progress to infectious endometritis (Christoffersen & Troedsson, 2017; Hughes & Loy, 1969). Bacteria are introduced into the female genital tract at mating, ascend from the vagina or may be activated from a dormant state within the endometrium (Davis et al., 2013; Petersen et al., 2015). The most common bacteria isolated from the uteri of mares are *E. coli* and *S. zooepidemicus* (Christoffersen et al., 2015b; Davis et al., 2013; LeBlanc & Causey, 2009). *Streptococcus zooepidemicus* is one of several β -haemolytic streptococci associated with infectious endometritis. Specific reproductive strains of *S. zooepidemicus* are opportunistic and reside in the caudal reproductive tract until they produce disease in response to tissue damage (Timoney, 2004). They belong to a genetically distinct subpopulation (Christoffersen et al., 2015b; Rasmussen et al., 2013) and persist deep in the endometrial tissue (Petersen et al., 2015; Skive et al., 2017) in chronically infected mares. They are not detectable by standard bacterial culture techniques but can be activated by PBIE and acute infectious endometritis may develop (Petersen et al., 2015).

Despite the frequent isolation of *E. coli* from mares with endometritis, no uterine-specific strains have been identified in horses so far. This suggests that *E. coli* are most likely contaminants and do not reside in the equine uterus. In addition to *E. coli* and *S. zooepidemicus*, other bacteria, fungi and yeasts may also cause infectious endometritis. They may be iatrogenically introduced environmental contaminants, venereal pathogens or occur secondary to over-treatment with antibiotics.

In mares, contagious equine metritis (CEM) is caused by a microaerophilic gram-negative coccobacillus, *Taylorella equigenitalis*, also known as CEM organism (CEMO). Mating by stallions where the external genitalia are colonized with CEMO will almost always result in acute endometritis as will insemination with contaminated semen. The condition is considered a venereal disease (Timoney & Powell, 1988) and will not be discussed here.

4.3 | Sow endometritis: Pathogenesis

Most often, endometritis in sows is bacterial-induced, due to a delay in uterine involution, unhygienic insemination or contaminated semen, obstetrical intervention, dysfunction of the immune system

and/or inadequate myometrial contractility (Miciński et al., 2022). In addition, an association between urinary tract infection and endometritis has been described (Glock & Bilkei, 2005; Grahofer et al., 2013; Sipos et al., 2014).

Uterine resistance to infection is highest at oestrus (or before farrowing) when plasma levels of oestrogens are high and progesterone is low (Dalín et al., 2004). High concentrations of oestrogens lead to an increased migration of PMNs (and enhanced phagocytosis) into the endometrium and the lumen of the uterus thus enhancing uterine clearance (de Winter et al., 1994). Therefore, insemination after ovulation, which is considered untimely and incorrect, can lead to endometritis in sows, because progesterone concentration is increasing and hence detrimental to the uterine immune activity (Dalín et al., 1997; Kaeoket et al., 2005). In addition, the peripartum period is crucial for uterine health in sows. Particularly, prolonged farrowing (> 300 min from first to last born piglet), manual obstetrical intervention, the number of stillborn piglets and retained placentas are associated with intrauterine fluid and often, puerperal metritis (Björkman et al., 2018; Grahofer et al., 2022). Furthermore, duration of placental shedding (first to last placenta), obstetrical intervention and fever after farrowing significantly increase the amount of vaginal discharge in the puerperium and negatively influence the uterine involution (Egli et al., 2022; Grahofer et al., 2021; Meile et al., 2020; Trachsel et al., 2021). A seasonal effect for the development of endometritis in sows is described with the highest incidence between August and October (Dalín et al., 1997). Recently, two studies proposed that the vaginal microbiota can impact uterine health and lead to endometritis (Liang et al., 2022; Wang et al., 2017).

4.4 | Bitch endometritis: Pathogenesis

Although the pathogenesis of mating-induced endometritis in bitches is unknown, England et al. (2021) recently proposed that, at least for bitches with endometrial hyperplasia, there is delayed clearance of fluid from the uterus after breeding, mediated by a physical obstruction to fluid flow and reduced uterine contractions. They related these findings to a greater PMN influx following mating and lower fertility; suggesting that a hostile uterine environment affects the embryos when they enter the uterus. Within the same hypothesis England et al. (2021) also remarked on the early work from Dow (1959) and recent studies from García Mitacek et al. (2017) and Praderio et al. (2019) and proposed that it was also feasible that bacterial contamination of the uterus occurred through the open cervix in the absence of mating; suggesting that both mating-induced endometritis and postoestrous endometritis occur in the bitch.

It would seem probable that cases of chronic endometritis occur where either mating-induced or postoestrous endometritis persists throughout the luteal phase and anoestrus. Presumably also when bacteria enter the uterus postpartum (and may cause metritis) it is also possible that an endometritis is established, and that such endometritis could become chronic. For chronic cases of endometritis,

there are no data to suggest how many persisted following mating-induced endometritis, postoestrous endometritis or postpartum metritis/endometritis.

4.5 | Pathogenesis: Comparative aspects

The time point of occurrence of endometritis clearly differs among the described domestic species. In mares and bitches, mating-induced endometritis is most prevalent, whereas in cows and sows, postpartum endometritis is most common. There are, however, similarities in the pathogenesis of endometritis among species namely dysfunction of the immune response and overgrowth of pathogenic bacteria within the uterine cavity. In the dairy cow, immune dysfunction is more relevant due to the metabolic stress associated with high milk production after calving. In this regard, immune dysfunction itself has been associated with a form of sterile endometritis or SCE. Metabolic stress due to high energetic demands during late gestation and early lactation leading to immune dysfunction of the urogenital tract is also described in hyperprolific sows. In-depth knowledge of the mechanisms associated with endometritis is available in cows and mares whereas the knowledge on the genesis of endometritis in sows and bitches is rather hypothetical and thus remains obscure.

5 | PREVENTION

Adopting preventive strategies for endometritis largely depends on understanding their risk factors. Controlling for adequate feeding, hygiene, prolonged or traumatic parturition, timely obstetrical intervention, and monitoring for retained placenta is key to maintain a low prevalence of endometritis. Although immunomodulatory (including NSAIDs) and ecobolic therapies can be applied to reduce the incidence of endometritis, particularly in cows and horses, management is the most important factor for the avoidance of the disease in all domestic species. An interesting line of research that is under development and is not implemented in practice yet (but has a tremendous potential) is the adoption of pre-, pro- and postbiotics therapy to control the incidence of uterine diseases. Probiotics are live microorganisms that when administered to the host in proper amounts confer a protective effect or a health benefit (Fuller, 1989). Prebiotics promote the growth of beneficial microbes and postbiotics are the metabolites that probiotics produce to promote health (Scarpellini et al., 2021).

5.1 | Cow endometritis: Prevention

Purulent vaginal discharge and SCE are different manifestations of reproductive tract diseases. Yet, there are common risk factors for PVD and SCE such as metritis and excessive systemic inflammation characterized by high blood haptoglobin (acute phase protein) in

the first week following parturition (≥ 0.8 g/L) (Cheong et al., 2011; Dubuc et al., 2010b). Risk factors uniquely associated with SCE are those linked with negative energy balance maladaptation such as high circulating β -hydroxybutyrate or nonesterified fatty acids in the postpartum period (Cheong et al., 2011; Dubuc et al., 2010b; Pascottini & LeBlanc, 2020). Risk factors for PVD are those associated with trauma (e.g. dystocia, twins and retained placenta) that favour excessive bacterial growth and infection (Dubuc et al., 2010b; Kelly et al., 2020). Although there may be unique risk factors for PVD and SCE, the best way to control their incidence is by adopting general managerial practices such as adequate body condition score before calving (between 3 and 3.5 on the scale from 1 to 5), hygiene in the calving and fresh cow pens, ad libitum access to fresh feed (timely delivered), provide space for lying, minimize social stress (overstocking and constant pen moving), provide heat abatement (adequate air circulation and water sprinklers), and monitor and control drastic BCS changes (LeBlanc et al., 2011; Pascottini et al., 2017; Sheldon et al., 2020).

Modulation of the immune function is key to safeguarding uterine health. In this regard, there are emerging lines of investigation that aid to mitigate impaired immune function in the transition period including preventive anti-inflammatory therapy, peripartum administration of granulocyte colony-stimulating factor, intrauterine recombinant IL-8 and modulation of calcium metabolism in the form of anionic salts, among others. The action and potential applications of these immune modulators were recently reviewed by Pascottini & LeBlanc (2020). In terms of probiotics, although there is a lack of dominance of lactogenic bacteria in the genital tract of dairy cows, they may confer a local, beneficial immune modulatory effect. In humans, it has been shown that probiotics-derived metabolites and extracellular vesicles can interact with host cell receptors and prime (or modulate) local immunity (Morishita et al., 2021; Perdigon et al., 1995). In vitro studies with bovine endometrial epithelial cells revealed that lactic acid bacteria alleviate inflammation induced by *E. coli* infection by reducing the production of pro-inflammatory cytokines (Genís et al., 2017). Proof of concept field studies showed an association between intravaginal administration of probiotics around calving and reduced incidence of uterine diseases (Ametaj et al., 2014; Deng et al., 2016). It is, perhaps, still unclear whether the vaginal administration of probiotics can gain access and perdure in the uterine cavity in the later stages of the postpartum period.

5.2 | Mare endometritis: Prevention

In mares susceptible to PBIE, enhancing physiological mechanisms of uterine clearance is the best method to prevent endometrial bacterial infection. Ecobolic treatment may be combined with uterine lavage to enhance mechanical clearance of the uterine lumen from debris and inflammatory material (LeBlanc & Causey, 2009; Pycock & Newcombe, 1996; Rose et al., 2018). Treatment with anti-inflammatory drugs, mucolytic agents and immunomodulators (Morris et al., 2020) aims at normalizing the immunological response

of the endometrium. Antibiotic treatment should not be a treatment option.

Ecbolic treatment in oestrous mares includes injection of oxytocin, PGF_{2α} and analogues. In addition, the oxytocin analogue carbetocin may be considered (Schramme et al., 2008). Treatment with PGF_{2α} and its analogues, however, should not be continued after ovulation because of detrimental effects on luteal development (Nie et al., 2003). The efficiency of ecbolic treatment is always limited in mares whose anatomical conditions impair uterine clearance. In such cases, uterine lavage may be beneficial (LeBlanc & Causey, 2009) and should always be considered when transrectal ultrasound examination demonstrates intrauterine fluid accumulation that exceeds 2 cm in diameter. Sterile saline or lactated Ringer's solution is most appropriate in such cases (Allen et al., 2007; LeBlanc & Causey, 2009).

Anti-inflammatory treatment may prevent excessive inflammation in mares with PBIE. There is evidence that both glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAID) reduce inflammation and may thus improve fertility when given at or prior to breeding (dexamethasone: Bucca et al., 2008; Dell'Aqua et al., 2006; NSAIDs: Friso et al., 2019; Rojer & Aurich, 2010). While treatment with the NSAID flunixin meglumine during the periovulatory period may inhibit ovulation and dexamethasone increase the inter-ovulatory interval (Martínez-Boví et al., 2023), application of the NSAID firocoxib reduced endometrial inflammation with no such adverse effects (Friso et al., 2019).

Under experimental conditions, immunomodulatory treatment with human recombinant lactoferrin (Fedorka et al., 2017), IL-6 (Coutinho da Silva et al., 2017) and endometrial mesenchymal stem cells (Felipe et al., 2020; Rink et al., 2018) demonstrated immunomodulatory and even antimicrobial properties and thus reduced the PMN influx during the endometrial response to mating. These substances are, however, not commercially available for veterinary treatment. Recently, plasma products have therefore gained increasing attention for the treatment of PBIE because such substances can be produced noncommercially. Among those, platelet-rich plasma has become quite popular (Segabinazzi, Canisso, et al., 2021). It includes various growth factors that may help to reduce endometritis in mares with PBIE (Reghini et al., 2016) and thus improve fertility (Segabinazzi, Podico, et al., 2021). Alternatively, intrauterine treatment with autologous conditioned serum (Ferris et al., 2014) or a platelet lysate produced by freeze-thawing platelets after concentration (Colombo et al., 2022) reduced the endometrial inflammation in mares. Similar success was reported after the treatment of mares with mycobacterium cell wall extract (Fumuso et al., 2007; Woodward et al., 2015). In conclusion, there is, apparently, a wide range of immunomodulating substances that may prove valuable for the treatment of PBIE in mares.

5.3 | Sow endometritis: Prevention

Reproductive disorders in swine are often related to suboptimal management procedures and other noninfectious factors (Grafofer

et al., 2020). Although endometritis is often infectious, several management measures on a herd level can be established to reduce the risk of uterine disorders in sows. Depending on the time point of occurrence in the reproductive cycle, concepts of prevention and control must be adapted. Proper housing hygiene, optimal air quality and airflow are factors that should be established in problem herds. Furthermore, mycotoxin contamination in feed and rooting material should be considered because of their potential utero-pathogenic effect (Kauffold & Wehrend, 2014).

Nonpuerperal endometritis is often related to an improper artificial insemination management (Carabin et al., 1995). Especially, a proper hygiene standard of the insemination unit, clean storage of the insemination equipment and dry cleaning of the vulva together with parting of the vulva lips during insertion of the catheter are crucial factors to reduce the risk for a vulvar discharge syndrome (Maes et al., 1999). In addition, contamination of the semen with pathogenic agents in artificial insemination and natural breeding must be also considered as a risk factor and should be ruled out in herds with endometritis (Arnold et al., 2021; Maes et al., 2008).

Puerperal endometritis is often associated with an improper farrowing management (Björkman & Grahofer, 2020; Grahofer et al., 2020). Especially, the prevalence of prolonged farrowing duration should be decreased by improving the crude fibre in the diet and water intake to reduce obstipation (Oliviero et al., 2010). In addition, an optimal body condition score and enough rooting material to express the nest-building behaviour, which positively influences the hormonal changes before farrowing, are measures that should be implemented on the farm (Björkman & Grahofer, 2020). Obstetrical interventions during farrowing should be limited and only applied if indicated, because of increased the risk of fever, higher amount of vaginal discharge and endometritis after parturition (Björkman et al., 2018; Egli et al., 2022; Grahofer et al., 2021). Treatment with oxytocin after farrowing seems to prevent endometritis in crated sows, whereas no effect in free-farrowing sows could be established (Björkman et al., 2018; Egli et al., 2022; Meile et al., 2020).

5.4 | Bitch endometritis: Prevention

There are no data describing methods for prevention or reduction of cases of endometritis in the bitch. Presumably, though techniques such as cleaning of the vulva and penis before mating, use of artificial insemination and use of semen extenders containing antimicrobial agents may reduce the risk of uterine contamination at mating and therefore the risk of mating-induced endometritis. While it might be suggested that not breeding from bitches with endometrial hyperplasia would reduce the risk of them developing an endometritis, it is worth noting that some bitches develop endometritis when not mated. It would seem plausible that various ecbolic, anti-inflammatory and immunomodulatory treatments could reduce the impact of introduced bacteria and seminal components similar to that described in the mare. These treatment options will no doubt be investigated in the future. It would seem likely that ensuring good

hygiene at whelping, avoiding prolonged or traumatic parturition and rapidly treating cases of retained placenta would reduce the risk of uterine contamination at parturition and therefore reduce the number of cases of postpartum metritis/endometritis.

5.5 | Prevention: Comparative aspects

In all domestic species, preventive measures are dependent on understanding and controlling risk factors causing endometritis (Figure 3). In livestock, housing and management conditions are essential for the prevention of endometritis. Especially, the feeding regime, hygiene level, insemination and birth management on herds are crucial for lowering the prevalence of endometritis. In horses, postmating ultrasound examination to identify (and treat) mares susceptible to PBIE is an important preventive strategy. In bitches, there are no research data available for the prevention of endometritis, but monitoring for vaginal discharge and uterine ultrasound postmating or postpartum is highly recommended. Further understanding of postpartum microbial dynamics that cause infections in the uterus will allow the development of novel prebiotics, probiotics, postbiotics and herbal therapeutics as alternatives to antibiotics to prevent (and treat) infections avoiding stimulating the threat of antibiotic resistance.

6 | THERAPY—WITH SOME EMPHASIS ON NONANTIBIOTIC TREATMENT

Antibiotic resistance might naturally occur, but indiscriminate antimicrobial use can exponentially accelerate the process. Nowadays, antibiotic resistance is one of the major global threats to health

and food security. For the agricultural sector, the World Health Organization (WHO) recommends avoiding antimicrobial use for growth promotion or preventing disease, and in the case of clinical disease, WHO actively promotes alternatives to antimicrobial treatments when available. In the majority of cases, endometritis in domestic animals is not a life-threatening disease, and antimicrobial therapy is mostly based on improving reproductive performance in future reproductive cycles. Yet, antimicrobial therapy is not the only available option, there are multiple emerging lines of research aiming to treat (and cure) endometritis in a more sustainable way.

6.1 | Cow endometritis: Therapy

Clinical endometritis and PVD result from dysbiosis with an increased relative abundance of pathogenic bacteria. So, it is understandable that local antimicrobial treatment after an accurate diagnosis of CE and PVD is a viable option. Indeed, there is evidence that cows with CE or PVD have better reproductive performance when treated with a single intrauterine infusion of cephalosporin (first-generation cephalosporin) at the time of its diagnosis, relative to receiving no treatment (Denis-Robichaud & Dubuc, 2015b; Lefebvre & Stock, 2012). However, as neither CE nor PVD is life-threatening conditions and due to the fact that antibiotic resistance is a serious public health issue, it can be debatable whether the usage of antimicrobial therapy for CE and PVD is a sustainable treatment. Some years ago, it was reported that one or two injections of prostaglandin-F₂α or its analogues improved reproductive performance and accelerated the healing of PVD; however, it was suggested that these trials lacked clear case disease definitions (PVD is not CE) or statistical power (LeBlanc et al., 2011). Further, review and meta-analysis studies did

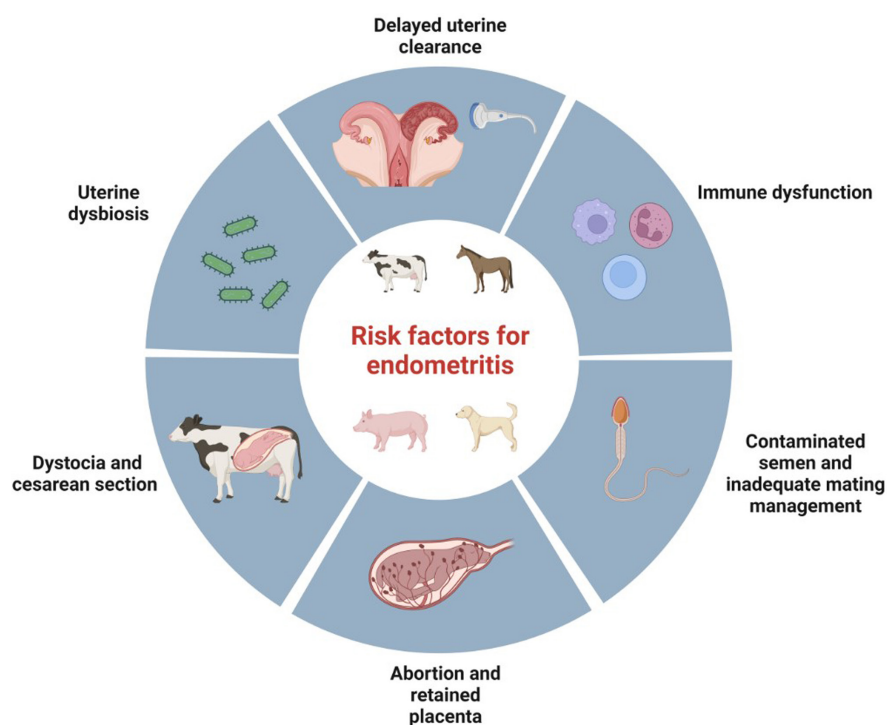


FIGURE 3 Schematic presentation of common risk factors associated with endometritis in domestic animals.

not reveal healing nor improvement of reproductive performance of cows with PVD or SCE after treatment with prostaglandin-F2 α (Haimel et al., 2013; Lefebvre & Stock, 2012).

Nonantibiotic therapy for CE and PVD has been considered by numerous authors. Intrauterine infusion of 50% dextrose (200 mL) had controversial results in the cure rate of PVD (Ahmadi et al., 2019; Brick et al., 2012; Machado et al., 2015) although in one study, fertility improved after treatment (Ahmadi et al., 2019). Intrauterine infusion of herbal extracts, ozone or analogous serum was experimented in other studies (Escandón et al., 2020; Eshghi et al., 2022; Heuwieser et al., 2000; Paiano & Baruselli, 2022), but again, most of them lacked statistical power or a proper study design (randomization and double-blinded design). Regarding SCE, surprisingly, one large and well-designed study found a benefit from the use of intrauterine cephalixin at SCE diagnosis on the first service conception rate (Denis-Robichaud & Dubuc, 2015b). Potentially, some cases of SCE may be associated with delayed uterine involution (cows recovering from metritis or CE) or simply because there was low accuracy of SCE diagnosis when performing (or evaluating) endometrial cytology (de Boer et al., 2014). Uterine flushing with saline solution may help to cleanse the uterus and reduce the proportion of inflammatory cells, but it is impractical as a field treatment (Dini et al., 2015). The use of probiotics as a co-adjuvant following intrauterine antimicrobials treatment (or any other treatment) to restore the uterine microbiota has not been explored yet. In short, a validated nonantibiotic treatment for CE, PVD or SCE is currently unavailable in practice.

6.2 | Mare endometritis: Therapy

Treatment with antibiotics requires evidence of bacterial infection by clinical signs, a positive bacterial culture plus an antimicrobial sensitivity test (Nocera et al., 2021). In mares, identification of the infectious agent is, perhaps, not always consistent with cytological evidence of inflammation (Davis et al., 2013).

Among veterinarians, there is often a preference for intrauterine antibiotic treatment of endometritis rather than a parenteral approach (LeBlanc & Causey, 2009). Intrauterine infusions produce high local concentrations of antibiotic in the uterine lumen (LeBlanc & Causey, 2009) but the efficiency of such treatment may be limited. An efficacy of systemic antibiotic treatment and the relationship between plasma and tissue concentrations was meanwhile demonstrated for several antibiotics in mares (Davolli et al., 2018; Scofield et al., 2014; Witte et al., 2010, 2018). Biofilm-producing bacteria may complicate an effective treatment and require disruption of the biofilm. Therefore, in such cases, antibiotic treatment should be combined with a treatment that disrupts biofilm, as for example, tris-EDTA or dimethyl sulfoxide (DMSO; Ferris et al., 2016; Loncar et al., 2017). Any treatment with biofilm-disrupting agent must take into account that the agent may reduce antibiotic activity.

Because of the growing awareness that any antibiotic treatment may contribute to the development of resistant bacteria, alternatives

require consideration. Enhancing the mechanical uterine clearance alone is unfortunately not always effective for the treatment of bacterial endometritis in horses (Li et al., 2021). Different nonantibiotic agents may have bacteriostatic properties in the uterus. This includes DMSO (Guo et al., 2016; Santos et al., 2003; Yahya et al., 2018), N-acetylcysteine (Caissie et al., 2020; Ferris et al., 2016; Melkus et al., 2013) and hydrogen peroxide (Ferris et al., 2016). More recently, the intrauterine application of ozone has gathered attention. Direct intrauterine ozone gas infusion was effective in treating endometritis in mares, reducing both endometrial inflammation and infection (Ávila et al., 2022).

Predominance of hydrogen peroxide producing *Lactobacillus* spp. in the vaginal flora may reflect a balance in natural immune systems in maintaining a healthy microbiome (Heil et al., 2018). The *Lactobacillus* spp. are present in the vagina of healthy mares and demonstrated some promising features for their use as equine probiotics (Fraga et al., 2008), but no recent information in this regard is available for the treatment of endometritis in horses. Recently, genome sequencing has identified Proteobacteria as the predominant species in the normal microbiota in fertile mares (Heil et al., 2018). In this context, it was suggested that any shift in endometrial microbiome of mares may lead to an increased risk of bacterial endometritis.

6.3 | Sow endometritis: Therapy

Treatment of endometritis in sows can be frustrating because the response of antimicrobials may be limited, and therefore, the reproductive performance will be still reduced (Ye et al., 2021). Hence, culling affected sows is most often a cost-effective alternative. It has been shown that administration of oxytocin after farrowing supports uterine involution in crated sows and therefore, might reduce the incidence of endometritis (Björkman et al., 2018). Several studies have evaluated the prophylactic treatment with NSAID during the peripartum period (Claeyé et al., 2015; Plush et al., 2021; Schoos et al., 2020; Ward et al., 2022; Will et al., 2023). Anti-inflammatory therapy can have a beneficial effect on the uterine health of the sows, but the effect seems to be depending on the herd and the management procedure. Recently, 400 U dosage (lysostaphin/pill/time) intravaginally applied in sows with endometritis showed a better cure rate than treatment with oxytetracycline (82 vs. 72%) (Ye et al., 2021). However, prevention measures to reduce the prevalence of endometritis on herd levels should be the goal.

6.4 | Bitch endometritis: Therapy

There is very limited work on the treatment of mating-induced endometritis in the bitch. However, a small number of studies have demonstrated that short-duration postmating administration of systemic antibiotic may increase pregnancy rates (England, Burgess et al., 2012; England, Moxon et al., 2012; England et al., 2021). It seems likely that such 'rescue' of fertility by postmating antibiotic is

possible because, in the absence of uterine inflammation at the time of breeding, sperm are harboured 'safely' within the distal utero-tubal junction and/or the uterine tube, and that the endometritis develops subsequent to sperm deposition and largely involves the uterus. Sperm therefore remain available for fertilization, and as long as the endometritis is resolved prior to the entrance of the fertilized embryos into the uterus, the pregnancy will be maintained. The use of antimicrobials in these cases has largely served to elucidate the role of bacteria in the aetiology of mating-induced endometritis in this species. Future work should focus on non-antimicrobial treatments such as enhancing uterine clearance. It might be proposed for example that uterine ecboic agents may also help clear trapped uterine fluid, but currently, there are no publications demonstrating such efficacy. Further work could also consider non-antibiotic agents, which are bacteriostatic. One further treatment option in this species that has received some anecdotal discussion, is the use of progesterone receptor antagonists. These drugs may block the action of progesterone, which is the significant hormone causing endometrial hyperplasia. The proposal is that the uterus may return to a more normal appearance if provided with rest from the action of progesterone.

Data for the treatment of chronic endometritis are scant. In a single case report, prebreeding treatment with systemic antibiotics, oxytocin and uterine lavage was successful in removing uterine fluid, and that repeated treatments postbreeding allowed the establishment of pregnancy (Lyman et al., 2018).

6.5 | Therapy: Comparative aspects

Significant differences in the therapeutic attempts in the described species are present, and legal requirements and economic factors also play a role. Especially, restrictions on antimicrobial usage in food animal production (cows, mares and sows) are established by authorities. Furthermore, the implementation of the 'One Health' approach to reducing antimicrobial resistance also includes companion animals (mares and bitches), and therefore, different alternative therapeutic approaches have also been studied in these species. Local antimicrobial treatment after an accurate diagnosis of CE and PVD is a viable option in cows. Alternatives have been studied but leading to controversial results. In mares, different non-antibiotic agents are used for treatment, but if antimicrobials are indicated due to the clinical status of the mare, systemic treatment may be preferred. In sows, the prophylactic usage of oxytocin and NSAID in the peripartum period leads to promising results in reducing the incidence of postpartum endometritis. Treatment concepts in bitches are rare and therefore therapy is given upon symptomatology in affected animals.

7 | CONCLUSIONS AND FUTURE PERSPECTIVES

Endometritis interferes with fertility in all domestic species and although there are similarities, some unique features can also be found.

For most cases, exudative discharge protruding through the vulvar commissure that exceeds the normal time of uterine involution, or several days after mating (or heat), is the most common indicative of endometritis. After parturition, however, there is a thin line between physiological and pathological endometritis and uterine involution timing differs among domestic species. Uterine involution is faster in mares and sows, which is mostly associated with the superficial type of placentation (epitheliochorial). In cows and bitches, the type of placentation is more invasive (synepitheliochorial and endothelichorial, respectively) and upon placental detachment, it produces disturbance to the integrity of the endometrium. Furthermore, in the cow, (mal) adaptation to metabolic stress associated with milk production plays a pivotal role in the modulation of immune function and proper uterine involution. In mares and bitches, and to a lesser degree in the sow, myometrial contractibility, genital tract and perineal conformation and probably some other individual factors play a key role in the avoidance of PBIE while this condition is not of clinical importance in the cow.

Prevention of endometritis largely depends on adequate management practices in cows and sows. This is directly associated with the production intensity in these species in which feeding, (over) stocking, environmental hygiene, air quality and ambient temperature may produce significant stress in the animals and compromise their immune capacity to tolerate and resist bacteria. In the mare, prevention is mostly linked with veterinary intervention in the form of foaling assistance, ecboic or uterine flushing therapy upon mating and sometimes corrective surgeries (e.g. vulvoplasty). In the bitch, preventive approaches are not well developed.

Antimicrobial usage should be minimized for the treatment of endometritis, and antimicrobial-based preventive strategies should be avoided in any case. Preventive and therapeutic use of immune modulators are being developed for cows and mares, and although some results are promising no conclusive data are supporting their clinical use yet. Pre-, pro- and postbiotics usage is re-emerging not only due to their capacity to inhibit the growth of potentially pathogenic bacteria but also because of their interaction with host tissues, thus immune modulatory properties. Even when good managerial practices and other preventive strategies are applied, some animals will still develop endometritis although to a lesser extent. Furthermore, to date, effective non-antibiotic therapy is not commercially available yet.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the manuscript.

ACKNOWLEDGEMENT

Open access funding provided by Universitat Bern.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

C. Aurich  <https://orcid.org/0000-0001-6077-7362>

A. Grahofer  <https://orcid.org/0000-0002-6030-3586>

REFERENCES

- Ahmadi, M. R., Makki, M., Mirzaei, A., & Gheisari, H. R. (2019). Effects of hypertonic dextrose and paraffin solution as non-antibiotic treatments of clinical endometritis on reproductive performance of high producing dairy cows. *Reproduction in Domestic Animals*, 54, 762–771. <https://doi.org/10.1111/rda.13424>
- Alghamdi, A. S., Foster, D. N., Carlson, C. S., & Troedsson, M. H. (2005). Nitric oxide levels and nitric oxide synthase expression in uterine samples from mares susceptible and resistant to persistent breeding-induced endometritis. *American Journal of Reproductive Immunology*, 53(5), 230–237. <https://doi.org/10.1111/j.1600-0897.2005.00270.x>
- Allen, W. R. (1993). Proceedings of the John P. Hughes International workshop on equine endometritis. Davis, California, August 1992. *Equine Veterinary Journal*, 25(3), 184–193. <https://doi.org/10.1111/j.2042-3306.1993.tb02940.x>
- Allen, W. R., Brown, L., Wright, M., & Wilsher, S. (2007). Reproductive efficiency of Flatrace and national hunt thoroughbred mares and stallions in England. *Equine Veterinary Journal*, 39(5), 438–445. <https://doi.org/10.2746/042516407x1737581>
- Ametaj, B. N., Iqbal, S., Selami, F., Odhiambo, J. F., Wang, Y., Gänzle, M. G., Dunn, S. M., & Zebeli, Q. (2014). Intravaginal administration of lactic acid bacteria modulated the incidence of purulent vaginal discharges, plasma haptoglobin concentrations, and milk production in dairy cows. *Research in Veterinary Science*, 96(2), 365–370. <https://doi.org/10.1016/j.rvsc.2014.02.007>
- Arnold, M., Richard, O., Gurtner, C., Nathues, H., & Grahofer, A. (2021). A case report: *Actinobaculum suis* infection associated with formation of pyogranuloma, epididymitis and azoospermia in a boar. *BMC Veterinary Research*, 17(1), 6. <https://doi.org/10.1186/s12917-020-02680-1>
- Ávila, A. C. A., Diniz, N. C., Serpa, R. T., de Castro Chaves, M. M. B., Viú, M. A., & de Oliveira, R. A. (2022). Effectiveness of ozone therapy in the treatment of endometritis in mares. *Journal of Equine Veterinary Science*, 112, 103900. <https://doi.org/10.1016/j.jevs.2022.103900>
- Barlund, C. S., Carruthers, T. D., Waldner, C. L., & Palmer, C. W. (2008). A comparison of diagnostic techniques for postpartum endometritis in dairy cattle. *Theriogenology*, 69(6), 714–723. <https://doi.org/10.1016/j.theriogenology.2007.12.005>
- Biksi, I., Takács, N., Vetési, F., Fodor, L., Szenci, O., & Fenyő, E. (2002). Association between endometritis and urocystitis in culled sows. *Acta Veterinaria Hungarica*, 50(4), 413–423. <https://doi.org/10.1556/AVet.50.2002.4.4>
- Björkman, S., & Grahofer, A. (2020). Tools and protocols for managing hyperprolific sows at parturition: optimizing piglet survival and sows' reproductive health. In F. Aral, R. Payan-Carreira, & M. Quaresma (Eds.), *Animal Reproduction in Veterinary Medicine*. IntechOpen.
- Björkman, S., Oliviero, C., Kauffold, J., Soede, N. M., & Peltoniemi, O. A. T. (2018). Prolonged parturition and impaired placenta expulsion increase the risk of postpartum metritis and delay uterine involution in sows. *Theriogenology*, 106, 87–92. <https://doi.org/10.1016/j.theriogenology.2017.10.003>
- Bogado Pascottini, O., Hostens, M., Sys, P., Vercauteren, P., & Opsomer, G. (2017). Cytological endometritis at artificial insemination in dairy cows: Prevalence and effect on pregnancy outcome. *Journal of Dairy Science*, 100(1), 588–597. <https://doi.org/10.3168/jds.2016-11529>
- Bondurant, R. H. (1999). Inflammation in the bovine female reproductive tract. *Journal of Animal Science*, 77(Suppl 2), 101–110. https://doi.org/10.2527/1999.77suppl_2101x
- Bonnett, B. N., Miller, R. B., Etherington, W. G., Martin, S. W., & Johnson, W. H. (1991). Endometrial biopsy in Holstein-Friesian dairy cows. I. Technique, histological criteria and results. *Canadian Journal of Veterinary Research*, 55(2), 155–161.
- Brick, T. A., Schuenemann, G. M., Bas, S., Daniels, J. B., Pinto, C. R., Rings, D. M., & Rajala-Schultz, P. J. (2012). Effect of intrauterine dextrose or antibiotic therapy on reproductive performance of lactating dairy cows diagnosed with clinical endometritis. *Journal of Dairy Science*, 95(4), 1894–1905. <https://doi.org/10.3168/jds.2011-4892>
- Bucca, S., Carli, A., Buckley, T., Dolci, G., & Fogarty, U. (2008). The use of dexamethasone administered to mares at breeding time in the modulation of persistent mating induced endometritis. *Theriogenology*, 70(7), 1093–1100. <https://doi.org/10.1016/j.theriogenology.2008.06.029>
- Bulun, S. E. (2009). Endometriosis. *The New England Journal of Medicine*, 360(3), 268–279. <https://doi.org/10.1056/NEJMra0804690>
- Caissie, M. D., Gartley, C. J., Scholtz, E. L., Hewson, J., Johnson, R., & Chenier, T. (2020). The effects of treatment with N-acetyl cysteine on clinical signs in persistent breeding-induced Endometritis susceptible mares. *Journal of Equine Veterinary Science*, 92, 103142. <https://doi.org/10.1016/j.jevs.2020.103142>
- Callahan, C. J., & Horstman, L. A. (1993). Treatment of postpartum metritis in dairy cows caused by *Actinomyces pyogenes*. *Bovine Practitioner*, 27, 162–164. <https://doi.org/10.21423/bovine-vol1993no27p162-165>
- Campbell, M. L., & England, G. C. (2004). Effect of teasing, mechanical stimulation and the intrauterine infusion of saline on uterine contractions in mares. *The Veterinary Record*, 155(4), 103–110. <https://doi.org/10.1136/vr.155.4.103>
- Carabin, H., Desnoyers, M., Vaillancourt, D., & Martineau, G. P. (1995). Influence of vulvar hygiene on cytology of vaginal smears after sham artificial insemination in sows. *Canadian Journal of Veterinary Research*, 59(3), 193–196.
- Carneiro, L. C., Cronin, J. G., & Sheldon, I. M. (2016). Mechanisms linking bacterial infections of the bovine endometrium to disease and infertility. *Reproductive Biology*, 16(1), 1–7. <https://doi.org/10.1016/j.repbio.2015.12.002>
- Chapwanya, A., Meade, K. G., Doherty, M. L., Callanan, J. J., Mee, J. F., & O'Farrelly, C. (2009). Histopathological and molecular evaluation of Holstein-Friesian cows postpartum: Toward an improved understanding of uterine innate immunity. *Theriogenology*, 71(9), 1396–1407. <https://doi.org/10.1016/j.theriogenology.2009.01.006>
- Cheong, S. H., Nydam, D. V., Galvão, K. N., Crosier, B. M., & Gilbert, R. O. (2011). Cow-level and herd-level risk factors for subclinical endometritis in lactating Holstein cows. *Journal of Dairy Science*, 94(2), 762–770. <https://doi.org/10.3168/jds.2010-3439>
- Christoffersen, M., Brandis, L., Samuelsson, J., Bojesen, A. M., Troedsson, M. H. T., & Petersen, M. R. (2015a). Diagnostic double-guarded low-volume uterine lavage in mares. *Theriogenology*, 83, 222–227. <https://doi.org/10.1016/j.theriogenology.2014.09.008>
- Christoffersen, M., Söderlind, M., Rudefalk, S. R., Pedersen, H. G., Allen, J., & Krekeler, N. (2015b). Risk factors associated with uterine fluid after breeding caused by streptococcus zooepidemicus. *Theriogenology*, 84(8), 1283–1290. <https://doi.org/10.1016/j.theriogenology.2015.07.007>
- Christoffersen, M., & Troedsson, M. (2017). Inflammation and fertility in the mare. *Reproduction in Domestic Animals*, 52(Suppl 3), 14–20. <https://doi.org/10.1111/rda.13013>
- Christoffersen, M., Woodward, E., Bojesen, A. M., Jacobsen, S., Petersen, M. R., Troedsson, M. H., & Lehn-Jensen, H. (2012). Inflammatory responses to induced infectious endometritis in mares resistant or

- susceptible to persistent endometritis. *BMC Veterinary Research*, 8, 41. <https://doi.org/10.1186/1746-6148-8-41>
- Claeyé, E., Beek, J., Meyns, T., & Maes, D. (2015). Effect of ketoprofen treatment in the prevention of postpartum dysgalactia syndrome in sows. *Vlaams Diergeneesk. Tijdschr.*, 84, 127–132. <https://doi.org/10.21825/VDV.84.127>
- Colombo, I., Mislei, B., Mari, G., Iacono, E., & Merlo, B. (2022). Effect of platelet lysate on uterine response of mares susceptible to persistent mating-induced endometritis. *Theriogenology*, 179, 204–210. <https://doi.org/10.1016/j.theriogenology.2021.12.001>
- Coutinho da Silva, M. A., Darr, C. R., Moraes, L. E., & Forshey, B. S. (2017). Lactoferrin modulates uterine inflammation postbreeding in the mare. *Journal of Equine Veterinary Science*, 56, 63–67. <https://doi.org/10.1016/j.jevs.2017.05.007>
- Dalin, A. M., Gidlund, K., & Eliasson-Selling, L. (1997). Post-mortem examination of genital organs from sows with reproductive disturbances in a sow-pool. *Acta Veterinaria Scandinavica*, 38(3), 253–262. <https://doi.org/10.1186/BF03548488>
- Dalin, A. M., Kaeoket, K., & Persson, E. (2004). Immune cell infiltration of normal and impaired sow endometrium. *Animal Reproduction Science*, 82–83, 401–413. <https://doi.org/10.1016/j.anireprosci.2004.04.012>
- Davis, H. A., Stanton, M. B., Thungrat, K., & Boothe, D. M. (2013). Uterine bacterial isolates from mares and their resistance to antimicrobials: 8,296 cases (2003–2008). *Journal of the American Veterinary Medical Association*, 242(7), 977–983. <https://doi.org/10.2460/javma.242.7.977>
- Davolli, G. M., Beavers, K. N., Medina, V., Sones, J. L., Pinto, C. R. F., Paccamonti, D. L., & Causey, R. C. (2018). Concentrations of sulfadiazine and trimethoprim in blood and endometrium of mares after administration of an oral suspension. *Journal of Equine Veterinary Science*, 67, 27–30. <https://doi.org/10.1016/j.jevs.2018.02.022>
- de Boer, M. W., LeBlanc, S. J., Dubuc, J., Meier, S., Heuwieser, W., Arlt, S., Gilbert, R. O., & McDougall, S. (2014). Invited review: Systematic review of diagnostic tests for reproductive-tract infection and inflammation in dairy cows. *Journal of Dairy Science*, 97(7), 3983–3999. <https://doi.org/10.3168/jds.2013-7450>
- de Winter, P. J., Verdonck, M., de Kruif, A., Devriese, L. A., & Haesebrouck, F. (1994). Influence of the oestrous cycle on experimental intrauterine *E. coli* infection in the sow. *Zentralblatt Für Veterinärmedizin. Reihe A*, 41(8), 640–644. <https://doi.org/10.1111/j.1439-0442.1994.tb00131.x>
- De Winter, P. J. J., Verdonck, M., de Kruif, A., Devriese, L. A., & Haesebrouck, F. (1995). Bacterial endometritis and vaginal discharge in the sow: Prevalence of different bacterial species and experimental reproduction of the syndrome. *Animal Reproduction Science*, 37, 325–335. [https://doi.org/10.1016/0378-4320\(94\)01342-J](https://doi.org/10.1016/0378-4320(94)01342-J)
- Deguaillume, L., Geffré, A., Desquilbet, L., Dizien, A., Thoumire, S., Vornière, C., Constant, F., Fournier, R., & Chastant-Maillard, S. (2012). Effect of endocervical inflammation on days to conception in dairy cows. *Journal of Dairy Science*, 95(4), 1776–1783. <https://doi.org/10.3168/jds.2011-4602>
- Dell'Aqua, J. A., Papa, F. O., Lopes, M. D., Alvarenga, M. A., Macedo, L. P., & Melo, C. M. (2006). Modulation of acute uterine inflammatory response after artificial insemination with equine frozen semen. *Animal Reproduction Science*, 94, 270–273.
- Deng, Q., Odhiambo, J. F., Farooq, U., Lam, T., Dunn, S. M., & Ametaj, B. N. (2016). Intravaginal probiotics modulated metabolic status and improved milk production and composition of transition dairy cows. *Journal of Animal Science*, 94(2), 760–770. <https://doi.org/10.2527/jas.2015-9650>
- Denis-Robichaud, J., & Dubuc, J. (2015a). Determination of optimal diagnostic criteria for purulent vaginal discharge and cytological endometritis in dairy cows. *Journal of Dairy Science*, 98(10), 6848–6855. <https://doi.org/10.3168/jds.2014-9120>
- Denis-Robichaud, J., & Dubuc, J. (2015b). Randomized clinical trial of intrauterine cephalirin infusion in dairy cows for the treatment of purulent vaginal discharge and cytological endometritis. *Journal of Dairy Science*, 98(10), 6856–6864. <https://doi.org/10.3168/jds.2014-9129>
- Dini, P., Farhoodi, M., Hostens, M., Van Eetvelde, M., Pascottini, O. B., Fazeli, M. H., & Opsomer, G. (2015). Effect of uterine lavage on neutrophil counts in postpartum dairy cows. *Animal Reproduction Science*, 158, 25–30. <https://doi.org/10.1016/j.anireprosci.2015.04.005>
- Dow, C. (1959). The cystic hyperplasia-pyometra complex in the bitch. *Journal of Comparative Pathology*, 69, 237–250. [https://doi.org/10.1016/s0368-1742\(59\)80023-0](https://doi.org/10.1016/s0368-1742(59)80023-0)
- Dubuc, J., Duffield, T. F., Leslie, K. E., Walton, J. S., & LeBlanc, S. J. (2010a). Definitions and diagnosis of postpartum endometritis in dairy cows. *Journal of Dairy Science*, 93(11), 5225–5233. <https://doi.org/10.3168/jds.2010-3428>
- Dubuc, J., Duffield, T. F., Leslie, K. E., Walton, J. S., & LeBlanc, S. J. (2010b). Risk factors for postpartum uterine diseases in dairy cows. *Journal of Dairy Science*, 93(12), 5764–5771. <https://doi.org/10.3168/jds.2010-3429>
- Egli, P. T., Schüpbach-Regula, G., Nathues, H., Ulbrich, S. E., & Grahofer, A. (2022). Influence of the farrowing process and different sow and piglet traits on uterine involution in a free farrowing system. *Theriogenology*, 182, 1–8. <https://doi.org/10.1016/j.theriogenology.2022.01.028>
- England, G. C., Burgess, C. M., & Freeman, S. L. (2012). Perturbed sperm-epithelial interaction in bitches with mating-induced endometritis. *Veterinary Journal (London, England: 1997)*, 194(3), 314–318. <https://doi.org/10.1016/j.tvjl.2012.04.031>
- England, G. C., Moxon, R., & Freeman, S. L. (2012). Delayed uterine fluid clearance and reduced uterine perfusion in bitches with endometrial hyperplasia and clinical management with postmating antibiotic. *Theriogenology*, 78(7), 1611–1617. <https://doi.org/10.1016/j.theriogenology.2012.07.009>
- England, G. C. W., Rijsselaere, T., Campbell, A., Moxon, R., & Freeman, S. L. (2021). Normal and abnormal response to sperm deposition in female dogs: A review and new hypotheses for endometritis. *Theriogenology*, 159, 176–183. <https://doi.org/10.1016/j.theriogenology.2020.10.013>
- Escandón, B. M., Espinoza, J. S., Perea, F. P., Quito, F., Ochoa, R., López, G. E., Galarza, D. A., & Garzón, J. P. (2020). Intrauterine therapy with ozone reduces subclinical endometritis and improves reproductive performance in postpartum dairy cows managed in pasture-based systems. *Tropical Animal Health and Production*, 52(5), 2523–2528. <https://doi.org/10.1007/s11250-020-02298-3>
- Eshghi, D., Kafi, M., Sharifiyazdi, H., Azari, M., Ahmadi, N., Ghasrodashti, A. R., & Sadeghi, M. (2022). Intrauterine infusion of blood serum of dromedary camel improves the uterine health and fertility in high producing dairy cows with subclinical endometritis. *Animal Reproduction Science*, 240, 106973. <https://doi.org/10.1016/j.anireprosci.2022.106973>
- Evans, M. J., Hamer, J. M., Gason, L. M., & Irvine, C. H. (1987). Factors affecting uterine clearance of inoculated materials in mares. *Journal of reproduction and fertility. Supplement*, 35, 327–334.
- Fedorka, C. E., Scoggin, K. E., Boakari, Y. L., Hoppe, N. E., Squires, E. L., Ball, B. A., & Troedsson, M. H. T. (2018). The anti-inflammatory effect of exogenous lactoferrin on breeding-induced endometritis when administered post-breeding in susceptible mares. *Theriogenology*, 114, 63–69. <https://doi.org/10.1016/j.theriogenology.2018.03.017>

- Fedorka, C. E., Scoggin, K. E., Woodward, E. M., Squires, E. L., Ball, B. A., & Troedsson, M. (2017). The effect of select seminal plasma proteins on endometrial mRNA cytokine expression in mares susceptible to persistent mating-induced endometritis. *Reproduction in Domestic Animals*, 52(1), 89–96. <https://doi.org/10.1111/rda.12813>
- Felipe, N., Saravia, F., Cisterna, G., Rojas, F., Silva Pedro, P., Rodriguez-Alvarez, L., Rojas, D., Cabezas, J., Mancanares, A. C., & Ovidio, C. F. (2020). Assessment of the anti-inflammatory and engraftment potential of horse endometrial and adipose mesenchymal stem cells in an in vivo model of post breeding induced endometritis. *Theriogenology*, 155, 33–42.
- Ferris, R. A., Frisbie, D. D., & McCue, P. M. (2014). Use of mesenchymal stem cells or autologous conditioned serum to modulate the inflammatory response to spermatozoa in mares. *Theriogenology*, 82(1), 36–42. <https://doi.org/10.1016/j.theriogenology.2014.02.015>
- Ferris, R. A., McCue, P. M., Borlee, G. I., Loncar, K. D., Hennes, M. L., & Borlee, B. R. (2016). In vitro efficacy of nonantibiotic treatments on biofilm disruption of gram-negative pathogens and an In vivo model of infectious Endometritis utilizing isolates from the equine uterus. *Journal of Clinical Microbiology*, 54(3), 631–639. <https://doi.org/10.1128/JCM.02861-15>
- Fontaine, E., Levy, X., Grellet, A., Luc, A., Bernex, F., Boulouis, H. J., & Fontbonne, A. (2009). Diagnosis of endometritis in the bitch: A new approach. *Reproduction in Domestic Animals*, 44(Suppl 2), 196–199. <https://doi.org/10.1111/j.1439-0531.2009.01376.x>
- Fraga, M., Perelmutter, K., Delucchi, L., Cidade, E., & Zunino, P. (2008). Vaginal lactic acid bacteria in the mare: Evaluation of the probiotic potential of native Lactobacillus spp. and Enterococcus spp. strains. *Antonie Van Leeuwenhoek*, 93(1–2), 71–78. <https://doi.org/10.1007/s10482-007-9180-4>
- Frazer, G. (2003). Post partum complications in the mare. Part 2: Fetal membrane retention and conditions of the gastrointestinal tract, bladder and vagina. *Equine Veterinary Education*, 15, 91–100.
- Friso, A. M., Segabinazzi, L. G. T. M., Cyrino, M., Correal, S. B., Freitas-Dell'Aqua, C. P., Teoro do Carmo, M., Dell'Aqua, J. A., Jr., Miró, J., Papa, F. O., & Alvarenga, M. A. (2019). Periovarian administration of firocoxib did not alter ovulation rates and mitigated post-breeding inflammatory response in mares. *Theriogenology*, 138, 24–30. <https://doi.org/10.1016/j.theriogenology.2019.06.045>
- Fuller, R. (1989). Probiotics in man and animals. *The Journal of Applied Bacteriology*, 66(5), 365–378.
- Fumuso, E. A., Aguilar, J., Giguère, S., Rivulgo, M., Wade, J., & Rogan, D. (2007). Immune parameters in mares resistant and susceptible to persistent post-breeding endometritis: Effects of immunomodulation. *Veterinary Immunology and Immunopathology*, 118(1–2), 30–39. <https://doi.org/10.1016/j.vetimm.2007.04.009>
- Galvão, K. N., Bicalho, R. C., & Jeon, S. J. (2019). Symposium review: The uterine microbiome associated with the development of uterine disease in dairy cows. *Journal of Dairy Science*, 102(12), 11786–11797. <https://doi.org/10.3168/jds.2019-17106>
- García Mitacek, M. C., Praderio, R. G., Stornelli, M. C., de la Sota, R. L., & Stornelli, M. A. (2017). Prostaglandin synthesis enzymes' gene transcription in bitches with endometritis. *Reproduction in Domestic Animals*, 52(Suppl 2), 298–302. <https://doi.org/10.1111/rda.12950>
- Genis, S., Sánchez-Chardi, A., Bach, A., Fàbregas, F., & Arís, A. (2017). A combination of lactic acid bacteria regulates *Escherichia coli* infection and inflammation of the bovine endometrium. *Journal of Dairy Science*, 100(1), 479–492. <https://doi.org/10.3168/jds.2016-11671>
- Gifford, A. T., Scarlett, J. M., & Schlafer, D. H. (2014). Histopathologic findings in uterine biopsy samples from subfertile bitches: 399 cases (1990–2005). *Journal of the American Veterinary Medical Association*, 244(2), 180–186. <https://doi.org/10.2460/javma.244.2.180>
- Gilbert, R. O. (2011). The effects of endometritis on the establishment of pregnancy in cattle. *Reproduction, Fertility, and Development*, 24(1), 252–257. <https://doi.org/10.1071/RD11915>
- Gilbert, R. O., & Santos, N. R. (2016). Dynamics of postpartum endometrial cytology and bacteriology and their relationship to fertility in dairy cows. *Theriogenology*, 85(8), 1367–1374. <https://doi.org/10.1016/j.theriogenology.2015.10.045>
- Gilbert, R. O., Shin, S. T., Guard, C. L., Erb, H. N., & Frajblat, M. (2005). Prevalence of endometritis and its effects on reproductive performance of dairy cows. *Theriogenology*, 64(9), 1879–1888. <https://doi.org/10.1016/j.theriogenology.2005.04.022>
- Glock, X. T., & Bilkei, G. (2005). The effect of postparturient urogenital diseases on the lifetime reproductive performance of sows. *The Canadian Veterinary Journal*, 46(12), 1103–1107.
- Gobikrushanth, M., Salehi, R., Ambrose, D. J., & Colazo, M. G. (2016). Categorization of endometritis and its association with ovarian follicular growth and ovulation, reproductive performance, dry matter intake, and milk yield in dairy cattle. *Theriogenology*, 86(7), 1842–1849. <https://doi.org/10.1016/j.theriogenology.2016.06.003>
- Grahofer, A., Björkman, S., & Peltoniemi, O. (2020). Diagnosis of endometritis and cystitis in sows: Use of biomarkers. *Journal of Animal Science*, 98(1), S107–S116. <https://doi.org/10.1093/jas/skaa144>
- Grahofer, A., Häberli, L., Nathues, H., & Kauffold, J. (2022). Kontinuierliche subjektive sonographische Graustufenanalyse der Uterusinvolutions von Zuchtsauen im puerperium [continuous, subjective sonographic grayscale analysis of uterine involution in sows during the postpartum period]. *Tierärztliche Praxis. Ausgabe G, Grosstiere/Nutztiere*, 50(1), 38–45. <https://doi.org/10.1055/a-1741-7855>
- Grahofer, A., Mäder, T., & Nathues, H. (2021). Evaluation of different point-of-care tests to characterize the vaginal discharge of sows after parturition and parameters' correlation with subsequent reproductive performance. *Porcine Health Management*, 7(1), 38. <https://doi.org/10.1186/s40813-021-00217-y>
- Grahofer, A., Sipos, S., Fischer, L., Entenfellner, F., & Sipos, W. (2013). Zystitiden der Zuchtsau – wie ist die Situation in Niederösterreich? *Klauentierpraxis*, 21, 27–29.
- Guo, Q., Wu, Q., Bai, D., Liu, Y., Chen, L., Jin, S., Wu, Y., & Duan, K. (2016). Potential Use of Dimethyl Sulfoxide in Treatment of Infections Caused by *Pseudomonas aeruginosa*. *Antimicrobial Agents and Chemotherapy*, 60(12), 7159–7169. <https://doi.org/10.1128/AAC.01357-16>
- Haimen, P., Heuwieser, W., & Arlt, S. (2013). Therapy of bovine endometritis with prostaglandin F2α: A meta-analysis. *Journal of Dairy Science*, 96(5), 2973–2987. <https://doi.org/10.3168/jds.2012-6154>
- Heil, B. A., Thompson, S. K., Kearns, T. A., Davolli, G. M., King, G., & Sones, J. L. (2018). Metagenetic characterization of the resident equine uterine microbiome using multiple techniques. *Journal of Equine Veterinary Science*, 66, 111.
- Heinonen, M., Leppävuori, A., & Pyörälä, S. (1998). Evaluation of reproductive failure of female pigs based on slaughterhouse material and herd record survey. *Animal Reproduction Science*, 52(3), 235–244. [https://doi.org/10.1016/s0378-4320\(98\)00105-5](https://doi.org/10.1016/s0378-4320(98)00105-5)
- Heuwieser, W., Tenhagen, B. A., Tischer, M., Lühr, J., & Blum, H. (2000). Effect of three programmes for the treatment of endometritis on the reproductive performance of a dairy herd. *The Veterinary Record*, 146(12), 338–341. <https://doi.org/10.1136/vr.146.12.338>
- Hughes, J. P., & Loy, R. G. (1969). Investigations on the effect on intra-uterine inoculation of streptococcus zooepidemicus in the mare. *Proceedings of the American Association of Equine Practitioners*, 15, 289–292.
- Ibrahim, M., Ferrer, M. S., Ellerbrock, R. E., & Rollin, E. (2021). Evaluation of mare endometrial cytology using the novel cytotope technique. *Animal Reproduction Science*, 230, 106770. <https://doi.org/10.1016/j.anireprosci.2021.106770>
- Kaeoket, K., Tantasuparuk, W., & Kunavongkrit, A. (2005). The effect of post-ovulatory insemination on the subsequent embryonic loss, oestrous cycle length and vaginal discharge in sows. *Reproduction in domestic animals = Zuchtthygiene*, 40(5), 492–494. <https://doi.org/10.1111/j.1439-0531.2005.00618.x>

- Kasimanickam, R., Duffield, T. F., Foster, R. A., Gartley, C. J., Leslie, K. E., Walton, J. S., & Johnson, W. H. (2004). Endometrial cytology and ultrasonography for the detection of subclinical endometritis in postpartum dairy cows. *Theriogenology*, 62(1-2), 9-23. <https://doi.org/10.1016/j.theriogenology.2003.03.001>
- Katila, T. (1995). Onset and duration of uterine inflammatory response of mares after insemination with fresh semen. *Biology of Reproduction*, 52(5), 515-517.
- Katila, T. (2016). Evaluation of diagnostic methods in equine endometritis. *Reproductive Biology*, 16(3), 189-196. <https://doi.org/10.1016/j.repbio.2016.06.002>
- Kauffold, J., Rautenberg, T., Hoffmann, G., Beynon, N., Schellenberg, I., & Sobiraj, A. (2005a). A field study into the appropriateness of transcutaneous ultrasonography in the diagnoses of uterine disorders in reproductively failed pigs. *Theriogenology*, 64(7), 1546-1558. <https://doi.org/10.1016/j.theriogenology.2005.03.022>
- Kauffold, J., & Wehrend, A. (2014). Fertilitätsstörungen beim weiblichen Schwein. Ursachen, Manifestation, Diagnostik und Vorgehen im Rahmen der tierärztlichen Bestandsbetreuung [Reproductive disorders in the female pig: causes, manifestation, diagnostics and approach in herd health care]. *Tierärztliche Praxis. Ausgabe G, Grosstiere/Nutztiere*, 42(3), 179-187.
- Kelly, E., McAloon, C. G., O'Grady, L., Duane, M., Somers, J. R., & Beltman, M. E. (2020). Cow-level risk factors for reproductive tract disease diagnosed by 2 methods in pasture-grazed dairy cattle in Ireland. *Journal of Dairy Science*, 103(1), 737-749. <https://doi.org/10.3168/jds.2019-17064>
- Kelley, D. E., Schnobrich, M. R., Gayer, S., Scoggin, C., Bradcamp, E., & Canisso, I. F. (2019). Leukocyte esterase reagent strips for stall-side diagnosis of endometritis in mares. *Journal of Equine Veterinary Science*, 81, 102672. <https://doi.org/10.1016/j.jevs.2019.01.009>
- Khan, F. A., Chenier, T. S., Murrant, C. L., Foster, R. A., Hewson, J., & Scholtz, E. L. (2017). Dose-dependent inhibition of uterine contractility by nitric oxide: A potential mechanism underlying persistent breeding-induced endometritis in the mare. *Theriogenology*, 90, 59-64. <https://doi.org/10.1016/j.theriogenology.2016.11.026>
- Koketsu, Y., Tani, S., & Iida, R. (2017). Factors for improving reproductive performance of sows and herd productivity in commercial breeding herds. *Porcine Health Management*, 3, 1. <https://doi.org/10.1186/s40813-016-0049-7>
- Kolaczowska, E., & Kubes, P. (2013). Neutrophil recruitment and function in health and inflammation. *Nature Reviews. Immunology*, 13(3), 159-175. <https://doi.org/10.1038/nri3399>
- LeBlanc, M. M. (2010). Advances in the diagnosis and treatment of chronic infectious and post-mating-induced endometritis in the mare. *Reproduction in domestic animals = Zuchtthygiene*, 45(Suppl 2), 21-27. <https://doi.org/10.1111/j.1439-0531.2010.01634.x>
- LeBlanc, M. M., Asbury, A. C., & Lyle, S. K. (1989). Uterine clearance mechanisms during the early postovulatory period in mares. *American Journal of Veterinary Research*, 50(6), 864-867.
- LeBlanc, M. M., & Causey, R. C. (2009). Clinical and subclinical endometritis in the mare: Both threats to fertility. *Reproduction in Domestic Animals*, 44(Suppl 3), 10-22. <https://doi.org/10.1111/j.1439-0531.2009.01485.x>
- Leblanc, M. M., Johnson, R. D., Calderwood-Mays, M. B., & Valderrama, C. (1995). Lymphatic clearance of India ink in reproductively normal mares and mares susceptible to endometritis. *Biology of Reproduction Monograph Series*, 1, 109-113.
- LeBlanc, S. J. (2014). Reproductive tract inflammatory disease in postpartum dairy cows. *Animal: An International Journal of Animal Bioscience*, 8(Suppl 1), 54-63. <https://doi.org/10.1017/S1751731114000524>
- LeBlanc, S. J., Duffield, T. F., Leslie, K. E., Bateman, K. G., Keefe, G. P., Walton, J. S., & Johnson, W. H. (2002). Defining and diagnosing postpartum clinical endometritis and its impact on reproductive performance in dairy cows. *Journal of Dairy Science*, 85(9), 2223-2236. [https://doi.org/10.3168/jds.S0022-0302\(02\)74302-6](https://doi.org/10.3168/jds.S0022-0302(02)74302-6)
- LeBlanc, S. J., Osawa, T., & Dubuc, J. (2011). Reproductive tract defense and disease in postpartum dairy cows. *Theriogenology*, 76(9), 1610-1618. <https://doi.org/10.1016/j.theriogenology.2011.07.017>
- Lefebvre, R. C., & Stock, A. E. (2012). Therapeutic efficiency of antibiotics and prostaglandin F2 α in postpartum dairy cows with clinical endometritis: An evidence-based evaluation. *The Veterinary Clinics of North America. Food Animal Practice*, 28(1), 79-ix. <https://doi.org/10.1016/j.cvfa.2012.01.002>
- Li, J., Zhao, Y., Gao, Y., Zhu, Y., Holyoak, G. R., & Zeng, S. (2021). Treatments for Endometritis in mares caused by *Streptococcus equi* subspecies zooepidemicus: A structured literature review. *Journal of Equine Veterinary Science*, 102, 103430. <https://doi.org/10.1016/j.jevs.2021.103430>
- Liang, H., Cai, R., Li, C., Glendon, O. H. M., Chengcheng, H., & Yan, H. (2022). High-throughput sequencing of 16S rRNA gene analysis reveals novel taxonomic diversity among vaginal microbiota in healthy and affected sows with endometritis. *Research in Veterinary Science*, 143, 33-40. <https://doi.org/10.1016/j.rvsc.2021.12.003>
- Lietaer, L., Bogado Pascottini, O., Heirbaut, S., Demeyere, K., Vandaele, L., Meyer, E., Fievez, V., Leroy, J. L. M. R., & Opsomer, G. (2023). Viability and function dynamics of circulating versus endometrial polymorphonuclear leukocytes in postpartum dairy cows with subclinical or clinical endometritis. *Journal of Dairy Science*, 106(5), 3436-3447. <https://doi.org/10.3168/jds.2022-22471>
- Lietaer, L., Pascottini, O. B., Heirbaut, S., Demeyere, K., Vandaele, L., Meyer, E., Fievez, V., & Opsomer, G. (2022). Quantitative and functional dynamics of circulating and endometrial polymorphonuclear leukocytes in healthy peripartum dairy cows. *Theriogenology*, 178, 50-59. <https://doi.org/10.1016/j.theriogenology.2021.11.002>
- Loncar, K. D., Ferris, R. A., McCue, P. M., Borlee, G. I., Hennes, M. L., & Borlee, B. R. (2017). In vitro biofilm disruption and bacterial killing using nonantibiotic compounds against gram-negative equine uterine pathogens. *Journal of Equine Veterinary Science*, 53, 94-99.
- López-Helguera, I., López-Gatius, F., & García-Ispuerto, I. (2012). The influence of genital tract status in postpartum period on the subsequent reproductive performance in high producing dairy cows. *Theriogenology*, 77(7), 1334-1342. <https://doi.org/10.1016/j.theriogenology.2011.10.038>
- Lyman, C. C., Hornberger, K. T., Hallman, R. M., & Holyoak, G. R. (2018). Theriogenology question of the month. *Journal of the American Veterinary Medical Association*, 253(10), 1267-1270. <https://doi.org/10.2460/javma.253.10.1267>
- Machado Pfeifer, L. F., de Souza Andrade, J., Moreira, E. M., Reis da Silva, R., Araújo Neves, P. M., Moreira da Silva, G., Lemos, I. C., & Schneider, A. (2018). Uterine inflammation and fertility of beef cows subjected to timed AI at different days postpartum. *Animal Reproduction Science*, 197, 268-277. <https://doi.org/10.1016/j.anireprosci.2018.08.039>
- Machado, V. S., Oikonomou, G., Bicalho, M. L., Knauer, W. A., Gilbert, R., & Bicalho, R. C. (2012). Investigation of postpartum dairy cows' uterine microbial diversity using metagenomic pyrosequencing of the 16S rRNA gene. *Veterinary Microbiology*, 159(3-4), 460-469. <https://doi.org/10.1016/j.vetmic.2012.04.033>
- Machado, V. S., Oikonomou, G., Ganda, E. K., Stephens, L., Milhomem, M., Freitas, G. L., Zinicola, M., Pearson, J., Wieland, M., Guard, C., Gilbert, R. O., & Bicalho, R. C. (2015). The effect of intrauterine infusion of dextrose on clinical endometritis cure rate and reproductive performance of dairy cows. *Journal of Dairy Science*, 98(6), 3849-3858. <https://doi.org/10.3168/jds.2014-9046>
- Maes, D., Nauwynck, H., Rijsselaere, T., Mateusen, B., Vyt, P., de Kruif, A., & Van Soom, A. (2008). Diseases in swine transmitted by artificial insemination: An overview. *Theriogenology*, 70(8), 1337-1345. <https://doi.org/10.1016/j.theriogenology.2008.06.018>

- Marth, C. D., Firestone, S. M., Hanlon, D., Glenton, L. Y., Browning, G. F., Young, N. D., & Krekeler, N. (2018). Innate immune genes in persistent mating-induced endometritis in horses. *Reproduction, Fertility, and Development*, 30(3), 533–545. <https://doi.org/10.1071/RD17157>
- Martínez-Boví, R., Plaza-Dávila, M., & Cuervo-Arango, J. (2023). The effect of dexamethasone and flunixin-meglumine on ovulation, endometrial oedema, and inter-ovulatory interval length in the mare. *Theriogenology*, 197, 57–61. <https://doi.org/10.1016/j.theriogenology.2022.11.042>
- McDougall, S., Macaulay, R., & Compton, C. (2007). Association between endometritis diagnosis using a novel intravaginal device and reproductive performance in dairy cattle. *Animal Reproduction Science*, 99(1–2), 9–23. <https://doi.org/10.1016/j.anireprosci.2006.03.017>
- Meile, A., Nathues, H., Kauffold, J., & Grahof, A. (2020). Ultrasonographic examination of postpartum uterine involution in sows. *Animal Reproduction Science*, 219, 106540. <https://doi.org/10.1016/j.anireprosci.2020.106540>
- Meira, E. B., Jr., Henriques, L. C., Sá, L. R., & Gregory, L. (2012). Comparison of ultrasonography and histopathology for the diagnosis of endometritis in Holstein-Friesian cows. *Journal of Dairy Science*, 95(12), 6969–6973. <https://doi.org/10.3168/jds.2011-4950>
- Melkus, E., Witte, T., Walter, I., Heuwieser, W., & Aurich, C. (2013). Investigations on the endometrial response to intrauterine administration of N-acetylcysteine in oestrous mares. *Reproduction in Domestic Animals*, 48(4), 591–597. <https://doi.org/10.1111/rda.12131>
- Miciński, B., Jana, B., & Całka, J. (2022). Uterine inflammation changes the expression of cholinergic neurotransmitters and decreases the population of AChE-positive, uterus-innervating neurons in the Paracervical ganglion of sexually mature gilts. *Animals*, 12(13), 1676. <https://doi.org/10.3390/ani12131676>
- Mir, F., Fontaine, E., Albaric, O., Greer, M., Vannier, F., Schlafer, D. H., & Fontbonne, A. (2013). Findings in uterine biopsies obtained by laparotomy from bitches with unexplained infertility or pregnancy loss: An observational study. *Theriogenology*, 79(2), 312–322. <https://doi.org/10.1016/j.theriogenology.2012.09.005>
- Miranda-CasoLuengo, R., Lu, J., Williams, E. J., Miranda-CasoLuengo, A. A., Carrington, S. D., Evans, A. C. O., & Meijer, W. G. (2019). Delayed differentiation of vaginal and uterine microbiomes in dairy cows developing postpartum endometritis. *PLoS One*, 14(1), e0200974. <https://doi.org/10.1371/journal.pone.0200974>
- Monteiro, M. S., Matias, D. N., Poor, A. P., Dutra, M. C., Moreno, L. Z., Parra, B. M., Silva, A. P. S., Matajira, C. E. C., de Moura Gomes, V. T., Barbosa, M. R. F., Sato, M. I. Z., & Moreno, A. M. (2022). Causes of sow mortality and risks to post-mortem findings in a Brazilian intensive swine production system. *Animals*, 12(14), 1804. <https://doi.org/10.3390/ani12141804>
- Morishita, M., Horita, M., Higuchi, A., Marui, M., Katsumi, H., & Yamamoto, A. (2021). Characterizing different probiotic-derived extracellular vesicles as a novel adjuvant for immunotherapy. *Molecular Pharmaceutics*, 18(3), 1080–1092. <https://doi.org/10.1021/acs.molpharmaceut.0c01011>
- Morris, L. H. A., McCue, P. M., & Aurich, C. (2020). Equine endometritis: a review of challenges and new approaches. *Reproduction (Cambridge, England)*, 160(5), R95–R110. <https://doi.org/10.1530/REP-19-0478>
- Moxon, R., Whiteside, H., & England, G. C. W. (2016). Prevalence of ultrasound-determined cystic endometrial hyperplasia and the relationship with age in dogs. *Theriogenology*, 86(4), 976–980. <https://doi.org/10.1016/j.theriogenology.2016.03.022>
- Muirhead, M. R. (1986). Epidemiology and control of vaginal discharges in the sow after service. *The Veterinary Record*, 119(10), 233–235. <https://doi.org/10.1136/vr.119.10.233>
- Nie, G. J., Johnson, K. E., Wenzel, J. G., & Braden, T. D. (2003). Luteal function in mares following administration of oxytocin, cloprostenol or saline on day 0, 1 or 2 post-ovulation. *Theriogenology*, 60(6), 1119–1125. [https://doi.org/10.1016/s0093-691x\(03\)00112-2](https://doi.org/10.1016/s0093-691x(03)00112-2)
- Nocera, F. P., D'Eletto, E., Ambrosio, M., Fiorito, F., Pagnini, U., & De Martino, L. (2021). Occurrence and antimicrobial susceptibility profiles of *Streptococcus equi* subsp. *zooepidemicus* strains isolated from mares with fertility problems. *Antibiotics (Basel, Switzerland)*, 11(1), 25. <https://doi.org/10.3390/antibiotics11010025>
- O'Leary, S., Jasper, M. J., Warnes, G. M., Armstrong, D. T., & Robertson, S. A. (2004). Seminal plasma regulates endometrial cytokine expression, leukocyte recruitment and embryo development in the pig. *Reproduction (Cambridge, England)*, 128(2), 237–247. <https://doi.org/10.1530/rep.1.00160>
- Oliviero, C., Heinonen, M., Valros, A., & Peltoniemi, O. (2010). Environmental and sow-related factors affecting the duration of farrowing. *Animal Reproduction Science*, 119(1–2), 85–91. <https://doi.org/10.1016/j.anireprosci.2009.12.009>
- Oliviero, C., Junnikkala, S., & Peltoniemi, O. (2019). The challenge of large litters on the immune system of the sow and the piglets. *Reproduction in Domestic Animals*, 54(Suppl 3), 12–21. <https://doi.org/10.1111/rda.13463>
- Paiano, R. B., & Baruselli, P. S. (2022). The use of herbal treatments as alternatives to control uterine diseases in dairy cows. *Tropical Animal Health and Production*, 54(2), 148. <https://doi.org/10.1007/s11250-022-03153-3>
- Palm, F., Walter, I., Budik, S., Kolodziejek, J., Nowotny, N., & Aurich, C. (2008). Influence of different semen extenders and seminal plasma on PMN migration and on expression of IL-1beta, IL-6, TNF-alpha and COX-2 mRNA in the equine endometrium. *Theriogenology*, 70(5), 843–851. <https://doi.org/10.1016/j.theriogenology.2008.04.054>
- Pascottini, O. B., Dini, P., Hostens, M., Ducatelle, R., & Opsomer, G. (2015). A novel cytologic sampling technique to diagnose subclinical endometritis and comparison of staining methods for endometrial cytology samples in dairy cows. *Theriogenology*, 84(8), 1438–1446. <https://doi.org/10.1016/j.theriogenology.2015.07.032>
- Pascottini, O. B., Hostens, M., Dini, P., Vandepitte, J., Ducatelle, R., & Opsomer, G. (2016a). Comparison between cytology and histopathology to evaluate subclinical endometritis in dairy cows. *Theriogenology*, 86(6), 1550–1556. <https://doi.org/10.1016/j.theriogenology.2016.05.014>
- Pascottini, O. B., Hostens, M., Dini, P., Vandepitte, J., Ducatelle, R., & Opsomer, G. (2016b). Distribution of inflammation and association between active and chronic alterations within the endometrium of dairy cows. *Reproduction in Domestic Animals*, 51(5), 751–757. <https://doi.org/10.1111/rda.12742>
- Pascottini, O. B., Hostens, M., Dini, P., Van Eetvelde, M., Vercauteren, P., & Opsomer, G. (2016c). Prevalence of cytological endometritis and effect on pregnancy outcomes at the time of insemination in nulliparous dairy heifers. *Journal of Dairy Science*, 99(11), 9051–9056. <https://doi.org/10.3168/jds.2016-11348>
- Pascottini, O. B., Hostens, M., Sys, P., Vercauteren, P., & Opsomer, G. (2017). Risk factors associated with cytological endometritis diagnosed at artificial insemination in dairy cows. *Theriogenology*, 92, 1–5. <https://doi.org/10.1016/j.theriogenology.2017.01.004>
- Pascottini, O. B., & LeBlanc, S. J. (2020). Modulation of immune function in the bovine uterus peripartum. *Theriogenology*, 150, 193–200. <https://doi.org/10.1016/j.theriogenology.2020.01.042>
- Pascottini, O. B., Leroy, J. L. M. R., & Opsomer, G. (2022). Maladaptation to the transition period and consequences on fertility of dairy cows. *Reproduction in Domestic Animals*, 57(Suppl 4), 21–32. <https://doi.org/10.1111/rda.14176>
- Pascottini, O. B., Van Schyndel, S. J., Spricigo, J. F. W., Rousseau, J., Weese, J. S., & LeBlanc, S. J. (2020). Dynamics of uterine microbiota in postpartum dairy cows with clinical or subclinical endometritis. *Scientific Reports*, 10(1), 12353. <https://doi.org/10.1038/s41598-020-69317-z>

- Peltoniemi, O., Yun, J., Björkman, S., & Han, T. (2021). Coping with large litters: The management of neonatal piglets and sow reproduction. *Journal of Animal Science and Technology*, 63(1), 1–15. <https://doi.org/10.5187/jast.2021.e3>
- Perdigon, G., Alvarez, S., Rachid, M., Agüero, G., & Gobbato, N. (1995). Immune system stimulation by probiotics. *Journal of Dairy Science*, 78(7), 1597–1606. [https://doi.org/10.3168/jds.S0022-0302\(95\)76784-4](https://doi.org/10.3168/jds.S0022-0302(95)76784-4)
- Petersen, M. R., Skive, B., Christoffersen, M., Lu, K., Nielsen, J. M., Troedsson, M. H., & Bojesen, A. M. (2015). Activation of persistent *Streptococcus equi* subspecies zooepidemicus in mares with subclinical endometritis. *Veterinary Microbiology*, 179(1–2), 119–125. <https://doi.org/10.1016/j.vetmic.2015.06.006>
- Pleticha, S., Drillich, M., & Heuwieser, W. (2009). Evaluation of the Metrichick device and the gloved hand for the diagnosis of clinical endometritis in dairy cows. *Journal of Dairy Science*, 92(11), 5429–5435. <https://doi.org/10.3168/jds.2009-2117>
- Plush, K. J., Pluske, J. R., Lines, D. S., Ralph, C. R., & Kirkwood, R. N. (2021). Meloxicam and dexamethasone administration as anti-inflammatory compounds to sows prior to farrowing does not improve lactation performance. *Animals*, 11(8), 2414. <https://doi.org/10.3390/ani11082414>
- Praderio, R. G., García Mitacek, M. C., Núñez Favre, R., Rearte, R., de la Sota, R. L., & Stornelli, M. A. (2019). Uterine endometrial cytology, biopsy, bacteriology, and serum C-reactive protein in clinically healthy diestrus bitches. *Theriogenology*, 131, 153–161. <https://doi.org/10.1016/j.theriogenology.2019.03.039>
- Pycoc, J. F., & Allen, W. E. (1990). Inflammatory components in uterine fluid from mares with experimentally induced bacterial endometritis. *Equine Veterinary Journal*, 22(6), 422–425. <https://doi.org/10.1111/j.2042-3306.1990.tb04309.x>
- Pycoc, J. F., & Newcombe, J. R. (1996). Assessment of the effect of three treatments to remove intrauterine fluid on pregnancy rate in the mare. *The Veterinary Record*, 138(14), 320–323. <https://doi.org/10.1136/vr.138.14.320>
- Rasmussen, C. D., Haugaard, M. M., Petersen, M. R., Nielsen, J. M., Pedersen, H. G., & Bojesen, A. M. (2013). *Streptococcus equi* subsp. zooepidemicus isolates from equine infectious endometritis belong to a distinct genetic group. *Veterinary Research*, 44(1), 26. <https://doi.org/10.1186/1297-9716-44-26>
- Ravaioli, V., Raffini, E., Tamburini, M., Galletti, G., & Frasnelli, M. (2022). Infectious endometritis in mares: Microbiological findings in field samples. *Journal of Equine Veterinary Science*, 112, 103913. <https://doi.org/10.1016/j.jevs.2022.103913>
- Recuero, S., Sánchez, J. M., Mateo-Otero, Y., Bagés-Arnal, S., McDonald, M., Behura, S. K., Spencer, T. E., Kenny, D. A., Yeste, M., Lonergan, P., & Fernandez-Fuertes, B. (2020). Mating to intact, but not vasectomized, males elicits changes in the endometrial transcriptome: Insights from the bovine model. *Frontiers in Cell and Development Biology*, 8, 547. <https://doi.org/10.3389/fcell.2020.00547>
- Reghini, M. F., Ramires Neto, C., Segabinazzi, L. G., Castro Chaves, M. M., Dell'Aqua, C. d P., Bussiere, M. C., Dell'Aqua, J. A., Jr., Papa, F. O., & Alvarenga, M. A. (2016). Inflammatory response in chronic degenerative endometritis mares treated with platelet-rich plasma. *Theriogenology*, 86(2), 516–522. <https://doi.org/10.1016/j.theriogenology.2016.01.029>
- Ricci, A., Bonizzi, G., Sarasso, G., Gallo, S., Dondo, A., Zoppi, S., & Vincenti, L. (2017). Subclinical endometritis in beef cattle in early and late postpartum: Cytology, bacteriology, haptoglobin and test strip efficiency to evaluate the evolution of the disease. *Theriogenology*, 94, 86–93. <https://doi.org/10.1016/j.theriogenology.2017.02.006>
- Ricci, A., Gallo, S., Molinaro, F., Dondo, A., Zoppi, S., & Vincenti, L. (2015). Evaluation of subclinical endometritis and consequences on fertility in piedmontese beef cows. *Reproduction in Domestic Animals*, 50(1), 142–148. <https://doi.org/10.1111/rda.12465>
- Riddle, W. T., LeBlanc, M. M., & Stromberg, A. J. (2007). Relationships between uterine culture, cytology and pregnancy rates in a Thoroughbred practice. *Theriogenology*, 68(3), 395–402. <https://doi.org/10.1016/j.theriogenology.2007.05.050>
- Rigby, S. L., Barhoumi, R., Burghardt, R. C., Collieran, P., Thompson, J. A., Varner, D. D., Blanchard, T. L., Brinsko, S. P., Taylor, T., Wilkerson, M. K., & Delp, M. D. (2001). Mares with delayed uterine clearance have an intrinsic defect in myometrial function. *Biology of Reproduction*, 65(3), 740–747. <https://doi.org/10.1095/biolreprod65.3.740>
- Rink, B. E., Beyer, T., French, H. M., Watson, E., Aurich, C., & Donadeu, F. X. (2018). The fate of autologous endometrial mesenchymal stromal cells after application in the healthy equine uterus. *Stem Cells and Development*, 27(15), 1046–1052. <https://doi.org/10.1089/scd.2018.0056>
- Risco, A. M., Reilas, T., Muilu, L., Kareskoski, M., & Katila, T. (2009). Effect of oxytocin and flunixin meglumine on uterine response to insemination in mares. *Theriogenology*, 72(9), 1195–1201. <https://doi.org/10.1016/j.theriogenology.2009.07.012>
- Rojer, H., & Aurich, C. (2010). Treatment of persistent mating-induced endometritis in mares with the non-steroid anti-inflammatory drug vedaprofen. *Reproduction in Domestic Animals*, 45(6), e458–e460. <https://doi.org/10.1111/j.1439-0531.2009.01572.x>
- Rose, B. V., Firth, M., Morris, B., Roach, J. M., Wathes, D. C., Verheyen, K. L. P., & de Mestre, A. M. (2018). Descriptive study of current therapeutic practices, clinical reproductive findings and incidence of pregnancy loss in intensively managed thoroughbred mares. *Animal Reproduction Science*, 188, 74–84. <https://doi.org/10.1016/j.anireprosci.2017.11.011>
- Santos, N. C., Figueira-Coelho, J., Martins-Silva, J., & Saldanha, C. (2003). Multidisciplinary utilization of dimethyl sulfoxide: Pharmacological, cellular, and molecular aspects. *Biochemical Pharmacology*, 65(7), 1035–1041. [https://doi.org/10.1016/s0006-2952\(03\)00002-9](https://doi.org/10.1016/s0006-2952(03)00002-9)
- Santos, N. R., Lamb, G. C., Brown, D. R., & Gilbert, R. O. (2009). Postpartum endometrial cytology in beef cows. *Theriogenology*, 71(5), 739–745. <https://doi.org/10.1016/j.theriogenology.2008.09.043>
- Sartori, R., Gimenes, L. U., Monteiro, P. L., Jr., Melo, L. F., Baruselli, P. S., & Bastos, M. R. (2016). Metabolic and endocrine differences between *Bos taurus* and *Bos indicus* females that impact the interaction of nutrition with reproduction. *Theriogenology*, 86(1), 32–40. <https://doi.org/10.1016/j.theriogenology.2016.04.016>
- Šavc, M., Duane, M., O'Grady, L. E., Somers, J. R., & Beltman, M. E. (2016). Uterine disease and its effect on subsequent reproductive performance of dairy cattle: A comparison of two cow-side diagnostic methods. *Theriogenology*, 86(8), 1983–1988. <https://doi.org/10.1016/j.theriogenology.2016.06.018>
- Scarpellini, E., Rinninella, E., Basilico, M., Colomier, E., Rasetti, C., Larussa, T., Santori, P., & Abenavoli, L. (2021). From pre- and probiotics to post-biotics: A narrative review. *International Journal of Environmental Research and Public Health*, 19(1), 37. <https://doi.org/10.3390/ijerph19010037>
- Schoos, A., Chantziaras, I., Vandenabeele, J., Biebaut, E., Meyer, E., Cools, A., Devreese, M., & Maes, D. (2020). Prophylactic use of meloxicam and paracetamol in Periparturient sows suffering from postpartum Dysgalactia syndrome. *Frontiers in Veterinary Science*, 7, 603719. <https://doi.org/10.3389/fvets.2020.603719>
- Schramme, A. R., Pinto, C. R., Davis, J., Whisnant, C. S., & Whitacre, M. D. (2008). Pharmacokinetics of carbetocin, a long-acting oxytocin analogue, following intravenous administration in horses. *Equine Veterinary Journal*, 40(7), 658–661. <https://doi.org/10.2746/042516408x334343>
- Scofield, D., Black, J., Wittenburg, L., Gustafson, D., Ferris, R., Hatzel, J., Traub-Dargatz, J., & McCue, P. (2014). Endometrial tissue and blood plasma concentration of ceftiofur and metabolites following intramuscular administration of ceftiofur crystalline free acid to mares. *Equine Veterinary Journal*, 46(5), 606–610. <https://doi.org/10.1111/evj.12192>

- Scott, C. J., de Mestre, A. M., Verheyen, K. L., & Arango-Sabogal, J. C. (2022). Bayesian accuracy estimates and fit for purpose thresholds of cytology and culture of endometrial swab samples for detecting endometritis in mares. *Preventive Veterinary Medicine*, 209, 105783. <https://doi.org/10.1016/j.prevetmed.2022.105783>
- Segabinazzi, L. G. T. M., Canisso, I. F., Podico, G., Cunha, L. L., Novello, G., Rosser, M. F., Loux, S. C., Lima, F. S., & Alvarenga, M. A. (2021). Intrauterine blood plasma platelet-therapy mitigates persistent breeding-induced Endometritis, reduces uterine infections, and improves embryo recovery in mares. *Antibiotics (Basel, Switzerland)*, 10(5), 490. <https://doi.org/10.3390/antibiotics10050490>
- Segabinazzi, L. G. T. M., Podico, G., Rosser, M. F., Nanjappa, S. G., Alvarenga, M. A., & Canisso, I. F. (2021). Three manual noncommercial methods to prepare equine platelet-rich plasma. *Animals*, 11(6), 1478. <https://doi.org/10.3390/ani11061478>
- Sheldon, I. M., Cronin, J. G., & Bromfield, J. J. (2019). Tolerance and innate immunity shape the development of postpartum uterine disease and the impact of Endometritis in dairy cattle. *Annual Review of Animal Biosciences*, 7, 361–384. <https://doi.org/10.1146/annurev-animal-020518-115227>
- Sheldon, I. M., Lewis, G. S., LeBlanc, S., & Gilbert, R. O. (2006). Defining postpartum uterine disease in cattle. *Theriogenology*, 65(8), 1516–1530. <https://doi.org/10.1016/j.theriogenology.2005.08.021>
- Sheldon, I. M., Molinari, P. C. C., Ormsby, T. J. R., & Bromfield, J. J. (2020). Preventing postpartum uterine disease in dairy cattle depends on avoiding, tolerating and resisting pathogenic bacteria. *Theriogenology*, 150, 158–165. <https://doi.org/10.1016/j.theriogenology.2020.01.017>
- Sipos, W., Grahofer, A., Fischer, L., Entenfellner, F., & Sipos, S. (2014). Keimspektrum des Urogenitaltraktes von Sauen mit Fertilitätsstörungen. *Wiener Tierärztliche Monatsschrift*, 101(9–10), 214–220.
- Skive, B., Rohde, M., Molinari, G., Braunstein, T. H., & Bojesen, A. M. (2017). *Streptococcus equi* subsp. *zoepidemicus* invades and survives in epithelial cells. *Frontiers in Cellular and Infection Microbiology*, 7, 465. <https://doi.org/10.3389/fcimb.2017.00465>
- Szenci, O., Sassi, G., Fodor, L., Molnár, L., Szelényi, Z., Tibold, J., Mádl, I., & Egyed, L. (2016). Co-infection with bovine herpesvirus 4 and *Histophilus somni* significantly extends the service period in dairy cattle with purulent vaginal discharge. *Reproduction in Domestic Animals*, 51, 143–149.
- Timoney, J. F. (2004). The pathogenic equine streptococci. *Veterinary Research*, 35(4), 397–409. <https://doi.org/10.1051/vetres:2004025>
- Timoney, P. J., & Powell, D. G. (1988). Contagious equine metritis—Epidemiology and control. *Journal of Equine Veterinary Science*, 8, 42–46.
- Trachsel, C., Küker, S., Nathues, H., & Grahofer, A. (2021). Influence of different sow traits on the expulsion and characteristics of the placenta in a free farrowing system. *Theriogenology*, 161, 74–82. <https://doi.org/10.1016/j.theriogenology.2020.11.023>
- Traub-Dargatz, J. L., Salman, M. D., & Voss, J. L. (1991). Medical problems of adult horses, as ranked by equine practitioners. *Journal of the American Veterinary Medical Association*, 198(10), 1745–1747.
- Troedsson, M. H. (1999). Uterine clearance and resistance to persistent endometritis in the mare. *Theriogenology*, 52(3), 461–471. [https://doi.org/10.1016/S0093-691X\(99\)00143-0](https://doi.org/10.1016/S0093-691X(99)00143-0)
- Valdmann, M., Kurykin, J., & Waldmann, A. (2022). Individual and combined effects of diseases and cytological Endometritis on reproductive performance and culling of dairy cows: Preliminary results. *Animals*, 12(21), 2913. <https://doi.org/10.3390/ani12212913>
- Van Schyndel, S. J., Bogado Pascottini, O., & LeBlanc, S. J. (2018). Comparison of cow-side diagnostic techniques for subclinical endometritis in dairy cows. *Theriogenology*, 120, 117–122. <https://doi.org/10.1016/j.theriogenology.2018.08.001>
- Wagener, K., Gabler, C., & Drillich, M. (2017). A review of the ongoing discussion about definition, diagnosis and pathomechanism of subclinical endometritis in dairy cows. *Theriogenology*, 94, 21–30. <https://doi.org/10.1016/j.theriogenology.2017.02.005>
- Waller, C. M., Bilkei, G., & Cameron, R. D. (2002). Effect of periparturient diseases accompanied by excessive vulval discharge and weaning to mating interval on sow reproductive performance. *Australian Veterinary Journal*, 80(9), 545–549. <https://doi.org/10.1111/j.1751-0813.2002.tb11033.x>
- Wang, J., Li, C., Nesengani, L. T., Gong, Y., Zhang, S., & Lu, W. (2017). Characterization of vaginal microbiota of endometritis and healthy sows using high-throughput pyrosequencing of 16S rRNA gene. *Microbial Pathogenesis*, 111, 325–330. <https://doi.org/10.1016/j.micpath.2017.08.030>
- Wang, M. L., Liu, M. C., Xu, J., An, L. G., Wang, J. F., & Zhu, Y. H. (2018). Uterine microbiota of dairy cows with clinical and subclinical Endometritis. *Frontiers in Microbiology*, 9, 2691. <https://doi.org/10.3389/fmicb.2018.02691>
- Wang, Y., Guo, H., Bai, Y., Li, T., Xu, R., Sun, T., Lu, J., & Song, Q. (2020). Isolation and characteristics of multi-drug resistant *Streptococcus porcinus* from the vaginal secretions of sow with endometritis. *BMC Veterinary Research*, 16(1), 146. <https://doi.org/10.1186/s12917-020-02365-9>
- Ward, S. A., Kirkwood, R. N., Song, Y., Garg, S., & Plush, K. J. (2022). Effect of dexamethasone and route of administration on sow farrowing Behaviours, piglet delivery and litter performance. *Animals*, 12(7), 847. <https://doi.org/10.3390/ani12070847>
- Watson, E. D., Barbacini, S., Berrocal, B., Sheerin, O., Marchi, V., Zavaglia, G., & Necchi, D. (2001). Effect of insemination time of frozen semen on incidence of uterine fluid in mares. *Theriogenology*, 56(1), 123–131. [https://doi.org/10.1016/S0093-691X\(01\)00548-9](https://doi.org/10.1016/S0093-691X(01)00548-9)
- Will, K. J., Magoga, J., De Conti, E. R., da Rosa Ulguim, R., Mellagi, A. P. G., & Bortolozzo, F. P. (2023). Relationship between dexamethasone treatment around parturition of primiparous sows and farrowing performance and newborn piglet traits. *Theriogenology*, 198, 256–263. <https://doi.org/10.1016/j.theriogenology.2022.12.044>
- Williams, E. J., Fischer, D. P., Pfeiffer, D. U., England, G. C., Noakes, D. E., Dobson, H., & Sheldon, I. M. (2005). Clinical evaluation of postpartum vaginal mucus reflects uterine bacterial infection and the immune response in cattle. *Theriogenology*, 63(1), 102–117. <https://doi.org/10.1016/j.theriogenology.2004.03.017>
- Witte, T., Hahn, K., & Duerr, S. (2018). Concentrations of gentamicin in serum, intrauterine fluid, and endometrial tissue after intravenous administration in healthy mares. *Journal of Equine Veterinary Science*, 66, 115.
- Witte, T. S., Bergwerff, A. A., Scherpenisse, P., Drillich, M., & Heuwieser, W. (2010). Ceftiofur derivatives in serum and endometrial tissue after intramuscular administration in healthy mares. *Theriogenology*, 74(3), 466–472. <https://doi.org/10.1016/j.theriogenology.2010.02.030>
- Woodward, E. M., Christoffersen, M., Campos, J., Betancourt, A., Horohov, D., Scoggin, K. E., Squires, E. L., & Troedsson, M. H. (2013). Endometrial inflammatory markers of the early immune response in mares susceptible or resistant to persistent breeding-induced endometritis. *Reproduction (Cambridge, England)*, 145(3), 289–296. <https://doi.org/10.1530/rep-12-0452>
- Woodward, E. M., Christoffersen, M., Horohov, D., Squires, E. L., & Troedsson, M. H. (2015). The effect of treatment with immune modulators on endometrial cytokine expression in mares susceptible to persistent breeding-induced endometritis. *Equine Veterinary Journal*, 47(2), 235–239. <https://doi.org/10.1111/evj.12266>
- Woodward, E. M., & Troedsson, M. H. (2015). Inflammatory mechanisms of endometritis. *Equine Veterinary Journal*, 47(4), 384–389. <https://doi.org/10.1111/evj.12403>

- Yahya, M. F. Z. R., Alias, Z., & Karsani, S. A. (2018). Antibiofilm activity and mode of action of DMSO alone and its combination with afatinib against Gram-negative pathogens. *Folia Microbiologica*, 63(1), 23–30. <https://doi.org/10.1007/s12223-017-0532-9>
- Ye, G., Huang, J., Li, G., Zhang, J., Sun, Y., Zeng, D., Bao, W., Zhong, J., & Huang, Q. (2021). Clinical efficacy of intravaginal recombinant lyso-staphin administration on endometritis in sows. *Veterinary Medicine and Science*, 7(3), 746–754. <https://doi.org/10.1002/vms3.417>

How to cite this article: Pascottini, O. B., Aurich, C., England, G., & Grahofer, A. (2023). General and comparative aspects of endometritis in domestic species: A review. *Reproduction in Domestic Animals*, 58(Suppl. 2), 49–71. <https://doi.org/10.1111/rda.14390>