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Risk factors of clinical and subclinical endometritis in cattle: a review

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Abstract: The postpartum period is a critical period in the life of dairy cattle and management of the most important problems and diseases at an early stage represents the key to successful dairy herd management. Endometritis is one of the most important and dramatic diseases that disrupt the reproductive performance of cows and reduce the livestock profitability. Because endometritis is a multifactorial disease and is caused by nonspecific bacteria, determining all the factors that enhance its risk of occurrence is more important than treating the disease. This review considers the evidence regarding the risk factors for postpartum endometritis in dairy cattle in an attempt to explain the causality between each risk factor and both clinical and subclinical endometritis. The present article will discuss the importance of determining the risk factors of endometritis that must be considered for the treatment of cows. For example, antibiotics must be associated with improvement of the rations in the case of nutritional deficit and metabolic problems. Furthermore, these risk factors represent an alternative to treatment by including them in an adequate preventive strategy to master at least the most important risk factor to limit the prevalence and severity of endometritis. We conclude that some factors are specific for one form of endometritis and some others are common between clinical and subclinical endometritis, but all of them make the disease more severe and frequent.

Key words: Clinical endometritis, dairy cattle, risk factor, subclinical endometritis

1. Introduction

In cows, 75% of cases of milk fever, ketosis, displaced abomasum, retained placenta, and uterine infections occur during the first 30 days postpartum (1). Interestingly, bacteria that are isolated from the uterine lumen of 80%–90% of normal cows during the first weeks after calving (2) are responsible for five ‘classifications’ of uterine infections: puerperal metritis, clinical metritis, clinical and subclinical endometritis, and pyometra.

Puerperal metritis presents as a fetid watery-red brown vulvar discharge associated with systemic signs and pyrexia (>39.5 °C) within 21 days of parturition, while clinical metritis presents as a purulent vulvar discharge detected within 21 days postpartum, but without any systemic signs (3). Clinical endometritis is characterized by purulent discharge after 21 days postpartum or a mucopurulent discharge after 26 days postpartum (3). In the absence of any clinical signs, subclinical endometritis is defined according to the stage of postpartum by the presence of >8% neutrophils in uterine cytological samples 21–33 days

postpartum, >6% neutrophils at 34–46 days postpartum, or >4% neutrophils after 48 days postpartum (4). Pyometra is characterized by a significant accumulation of purulent material in the uterine lumen combined with a closed cervix and the persistence of a corpus luteum (3).

The global incidence of endometritis in cattle is highly variable, ranging from 3.4% to 40%, depending on the diagnostic method (5). Clinical and subclinical endometritis negatively affect the performance of the world’s dairy industry; economic losses are related to delay in the resumption of ovarian activity, increased number of services per conception, decreased milk yield, and costs of treatment of the disease (6,7). The United States and Europe have 8.5 and 24.1 million dairy cows and uterine infection costs 650 million dollars and 1.4 billion Euros, respectively (2).

Excluding the bovine herpes virus 4 (BoHV-4), a large number of bacteria are responsible for clinical and subclinical endometritis (8,9); these are classified according to their pathogenicity and their frequency of

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isolation (Table 1) (8). *Escherichia coli* and *Trueperella pyogenes* are the most frequently isolated bacteria from the uterine lumen in cows with uterine infections, followed by anaerobic bacteria such as *Prevotella* spp., *Fusobacterium necrophorum*, and *Fusobacterium nucleatum* (3,5,9,10). Endometritis is considered to be a multifactorial disease with many factors having a direct or indirect, determining or predisposing influence (11,12). Interestingly, there are wide variations in results relating to risk factors for endometritis (1,12–15).

This review examines the evidence relating to risk factors for postpartum endometritis in dairy cattle in an attempt to explain the causality between each risk factor and both clinical and subclinical endometritis. It is hoped that this review will stimulate further studies of this condition that has a significant global impact, both in terms of loss of production and financial cost.

2. Risk factors

Importantly, the characteristics of the dairy herd can directly or indirectly affect the prevalence of endometritis (16). The farm is also considered as a risk factor for clinical and subclinical endometritis with an odds ratio (OR) of 1.1 (95% confidence interval (CI): 1.0–1.2) (10) (Table 2). Assuming that the prevalence of endometritis varies according to the method and the day of diagnosis (Table 2), the determination of the specific risk factors for clinical and subclinical endometritis will not be an easy matter.

In the current review, risk factors were categorized as extrinsic and intrinsic factors. Extrinsic factors concern all conditions and environmental characteristics shared by animals in the same herd, whereas intrinsic factors are specific variable characteristics of the individual cow.

2.1. Extrinsic factors

2.1.1. Calving season

A retrospective longitudinal study of postpartum uterine infections was performed in Denmark, where a significant correlation was found between clinical infection of the uterus during the first 30 days postpartum and calving

season (17) (Table 2). Although in the retrospective study it was not possible to distinguish between clinical endometritis and metritis, the authors reported that calving occurring between November and April dramatically increased the incidence of clinical infection of the uterus during the first month postpartum. This relationship may be explained by the fact that during the rainy seasons, the general health of cows decreases, making them more vulnerable to uterine infections (17–19). Ghavi Hossein-Zadeh and Ardalan (13), working on 57,301 dairy cows, confirmed the direct relation of causality between calving during winter months and clinical metritis (OR: 2.4). Metritis is considered to be one of the most important risk factors for clinical and subclinical endometritis (20), and calving season has an indirect significant effect on the incidence of clinical and subclinical endometritis (13).

Contrarily, other authors found that clinical endometritis (11) and subclinical endometritis (16) were not influenced by the season of calving. These divergent results can be explained by the fact that diagnostic criteria and climatic conditions were different between studies, especially, for example, the average environmental temperature, which was widely different between countries where the experimental works were conducted.

2.1.2. Nutrition

The quantity and quality of proteins included in the food ration play a key role in the efficiency of the immune system (21). Cellular immunity is also affected by protein quantity in food rations; protein deficiency dramatically reduces cellular phagocytosis (22). Noteworthy also is that excess protein intake induces high serum ammonia, which reduces lymphocyte production and favors the development of clinical endometritis (23).

Many vitamins are involved in the functioning of the immune system, including vitamins B and C, which have a role in antibody synthesis, and vitamin C, which ensures the integrity of immune cell membranes and protects them from free radicals (24). Deficiency of antioxidants contributes to prolonged and severe inflammation via

Table 1. Classification of bacteria isolated from the uterine lumen according to their potential pathogenicity (8).

Uterine pathogens	Potential pathogens	Opportunist contaminants
<i>Trueperella pyogenes</i> <i>Bacteroides</i> sp. <i>Prevotella melaninogenicus</i> <i>Escherichia coli</i> <i>Fusobacterium necrophorum</i>	<i>Bacillus licheniformis</i> <i>Enterococcus faecalis</i> <i>Mannheimia haemolytica</i> <i>Pasteurella multocida</i> <i>Peptostreptococcus</i> sp. <i>Staphylococcus aureus</i> Streptococci, nonhemolytic	<i>Clostridium perfringens</i> <i>Klebsiella pneumoniae</i> <i>Micrococcus</i> sp. <i>Proteus</i> sp. <i>Staphylococcus</i> sp., coagulase-negative α -Hemolytic streptococci <i>Streptococcus acidominimus</i> <i>Aspergillus</i> sp.

Table 2. Odds ratios of the risk factors of clinical and subclinical postpartum endometritis (CE: clinical endometritis, SCE: subclinical endometritis, MET: metritis, 95% CI: confidence interval at 95%).

Risk factor	Authors	Cow number	Odds ratio	Uterine infection form	95% CI
Herd					
	(10)	400	1.1	CE and SCE	1.0–1.2
Calving season					
Spring	(13)	57,301	1	MET	0.8–1.1
Summer			0.9		
Autumn			1.1		
Winter			2.4		
Cow's parity					
1	(17)	102,060	1	CE and MET*	0.8–1.2
	(12)	293	2.3	CE	1.2–4.4
	(13)	57,301	1.7	MET	1.5–1.8
2	(17)	102,060	0.6	CE and MET*	0.5–0.8
3			0.9		0.7–1.2
>4			1		
Calving conditions					
Dystocia	(42)	1374	4.9	CE and MET*	1.8–13.8
	(32)	7761	2.1	CE and MET*	1.6–2.8
	(58)	5278	1.4	CE and MET*	1–2.1
	(17)	102,060	3	CE and MET*	2.3–4
	(59)	441	2.2	CE	1.1–4.5
	(20)	1363	2.1	CE	1.4–4
	(12)	293	2.1	CE	1–4.4
	(13)	57,301	4.3	MET	3.7–4.9
	(30)	303	2.2	CE	1.1–4.6
Stillbirth	(43)	8521	2.9	MET	
	(32)	7761	1.5	CE and MET*	1.1–2.1
	(12)	293	7.5	CE	3–18.5
	(13)	57,301	6.3	MET	5.3–7.1
Male offspring	(12)	293	1.8	CE	1–3.3
	(13)	57,301	2.4	MET	2.1–2.7
Abortion	(58)	5278	2.4	CE and MET*	1–5.9
Twins	(43)	8521	2.3	MET	
	(20)	1363	2.2	CE	1.1–4.3
	(13)	57,301	6.6	MET	5.3–7.8
Retained placenta					
	(42)	1374	5.7	CE and MET*	3.6–8.8
	(32)	7761	6	CE and MET*	2.8–7.5
	(58)	5278	4.7	CE and MET*	3.5–6.5
	(11)	320	5.7	CE	3.1–10.4

Table 2. (Continued).

	(17)	102,060	Large** 9.9 Jersey 10.8	CE and MET*	6.9–14.1 6.4–18.3
	(60)	135	4.2	CE	1.0–18.1
	(12)	293	40.3	CE	5.0–326.4
	(59)	441	3.9	CE	1.6–7.4
	(13)	57,301	27.7	MET	24.5–30.8
Metritis					
	(20)	1363	2.3	CE	1.4–3.8
	(7)	779	1.9	SCE	1.0–3.3
	(30)	303	Clinical: 1.4 Puerperal: 2.2	CE	0.4–4.3 1.1–4.6
Metabolic disorders					
Ketosis	(11)	320	3.5	CE	1.1–10.8
	(59)	441	2.3	CE	1.1–4.5
	(43)	8521	2.5	MET	
	(32)	7761	1.7	CE and MET*	1–3
	(58)	5278	1.8	CE and MET*	1.2–2.7
	(17)	102,060	0.5	CE and MET*	0.2–1.3
	(7)	779	3.8	SCE	1.8–8.1
Milk fever	(43)	8521	1.8	MET	
	(11)	320	3.5	CE	1.1–10.8
Displaced abomasum	(42)	1374	3.6	CE and MET*	1.2–11.6
	(43)	8521	4.7	MET	1.1–10.8

*: Clinical endometritis and metritis were not differentiated and were considered as one outcome.

** : Large-breed cows (51% Holstein Friesians, 16% Red Holstein, 1.0% Danish Reds, and 9.5% cross-breed).

activation of the NF- κ B pathway and production of TNF, that latter also influencing insulin resistance and worsening energy deficiency (25). Vitamin A is important for epithelial tissue development and cell differentiation, which are very important in the early postpartum stage. Vitamin A also has immunological functions by increasing the early inflammatory phase through enhancing the number of macrophages at the site of a wound, which improves localization and stimulation of the immune response in the case of uterine infection (26).

A variety of minerals are involved in the uterine defense mechanisms. Calcium acts as complement-activator and calcium deficiency delays uterine involution and prolongs uterine infection. Calcium deficiency may be induced by excessive intake of phosphorus (27). Magnesium is involved in opsonization mechanisms (21). Selenium is involved in neutrophil function and its deficiency disrupts the reproductive performance of the cow and increases the risk of endometritis (28). Copper, zinc, and iron intervene in lysosome production and their deficiency dramatically

reduces phagocytosis and favors the growth of bacteria and development of clinical and subclinical endometritis (21,27).

2.2. Intrinsic factors

2.2.1. Parity of the cow

There are contradictory opinions concerning the relation between the presence of endometritis and parity. Some authors found no significant association between clinical endometritis and parity, except for primiparous cows and cows with more than five parturitions (29). Since primiparous cows are often subject to dystocia, endometrial lesions, and clinical endometritis, such a relationship is not surprising (12,17) (Table 2).

It appears clear that the duration of endometritis is related to the severity of initial uterine lesions. Older cows have reduced uterine elasticity and uterine involution is slower than in younger cows, which presumably increases the vulnerability of older cows to persistent uterine infection and endometritis. Balancing this effect, though, is the fact that in older cows there will have been

more episodes of uterine bacterial contamination, with the potential for some immunological resistance against uterine infection. In cases of bacterial contamination, older cows may efficiently and rapidly eliminate bacteria from the uterus while younger cows may have limited prior exposure, which delays the immune response, resulting in more severe and prolonged clinical and subclinical endometritis (29). Potter et al. (12) found primiparity in cows to be a risk factor for clinical endometritis with an OR of 2.3 ($P < 0.01$).

Persistent uterine infection and clinical endometritis were less frequent in primiparous than multiparous cows since uterine involution was more rapid in the primiparous group (11). However, Giuliadori et al. (30) and Thibier and Steffan (31) excluded an effect of the cow's age and parity number on the prevalence of clinical endometritis. Carneiro et al. (16) reported that parity did not affect the incidence of subclinical endometritis.

2.2.2. Dystocia

In cows, dystocia is often associated with multiple postpartum complications, for example retained fetal membranes and delayed uterine involution, both of which no doubt favor the development of endometritis (19,32). Within a retrospective study of 102,060 dairy cows, Bruun et al. (17) confirmed that dystocia was a risk factor that significantly increased the overall incidence of metritis and clinical endometritis during the first month after calving with an OR of 3.0 (95% CI: 2.3–4.0, $P < 0.001$) (Table 2). Giuliadori et al. (30) confirmed the correlation between abnormal calving and clinical endometritis with an adjusted OR of 2.2. Furthermore, dystocia indirectly increases the opportunity for the development of endometritis by increasing the probability of metritis with an OR of 4.3 (95% CI: 3.7–4.9, $P < 0.001$) (13). Abnormal calving and dystocia can induce trauma of the endometrium and calving assistance favors the introduction of bacteria into the uterus and increases the potential for clinical and subclinical endometritis to develop (17). Calving assistance encountered in the case of dystocia significantly increases the incidence of both clinical and subclinical endometritis (OR: 1.8; 95% CI: 1.2–3.0) (10). Potter et al. (12) also confirmed that calving assistance is a risk factor for clinical endometritis with an OR of 2.1 (95% CI: 1.0–4.4, $P > 0.05$).

Interestingly, the birth of a male calf, which is often larger than a female, may increase the risk of dystocia and thereby the risk of endometritis. Potter et al. (12) worked on 293 dairy cows and reported that the birth of a male calf was a risk factor for clinical endometritis with a relative risk of 1.5 (Table 2). These authors suggested that in the studied herd the prevalence of endometritis could be reduced by 60% if all calves born were female. The high incidence in male calves is related to their size, both increasing the risk

of dystocia and the subsequent need for calving assistance. Ghavi Hossein-Zadeh and Ardalan (13) confirmed this correlation with an OR of 2.4.

2.2.3. Retained placenta

Retained placental tissue represents the main important risk factor for endometritis in dairy cows (6,11,12). Other authors confirmed this causality in the case of metritis and clinical endometritis with ORs of 27.7 and 40.3, respectively (12,13) (Table 2). Residual tissue encountered in the case of a retained placenta represents a favorable medium for the growth of bacteria in the uterus and necrotic tissue delays uterine involution and the repair of the endometrium. Furthermore, residual tissues may result in the cervix being held open and an increase in bacterial contamination of the endometrium (11,12). Cows affected by endometritis have a very high concentration of bacterial lipopolysaccharide (LPS) and immune-depressant products that decrease the recruitment of leukocytes into the uterus to clear bacteria (2,33). A positive correlation between a retained placenta and subclinical endometritis seems to be due to the impairment of neutrophil function (14).

Indirectly, pregnancy length, induced calving, twins, and stillbirth increase the prevalence of clinical and subclinical endometritis by favoring the retention of fetal membranes. A study conducted on 2017 calvings distributed throughout 1 year concluded that primiparous cows with prolonged gestation (>270 days) had a greater risk of developing metritis and clinical endometritis than those with a normal length of gestation (19). Furthermore, multiparous cows with short gestation were more vulnerable to the most important risk factor for clinical and subclinical endometritis, a retained placenta, than those with prolonged gestation (12,34). Ghavi Hossein-Zadeh and Ardalan (13) reported that cows with short gestations (<270 days) were four times more likely to experience a retained placenta (OR: 3.8) than cows with a normal length of gestation (270–280 days).

Induced calving directly and indirectly affects the incidence of endometritis by increasing the risk for metritis, metabolic disorders, retained placenta, and stillbirth (34,35). The induction of calving using dexamethasone negatively affects chemotactic and phagocytosis activities, and, as a result, disengagement of cotyledons is reduced and retained placenta is favored, which increases the risk of developing clinical and subclinical endometritis (35).

The birth of twins has often been considered a risk factor for uterine infection as it can indirectly increase the prevalence of clinical and subclinical endometritis by favoring the development of other uterine diseases known as potential risk factors for endometritis. It seems that the incidence of retained placenta was higher in cows with twins than those with a single calf (35.7% vs.

7.7%, respectively) (36). Potter et al. (12) confirmed this observation and declared that the birth of twins was highly correlated with retained fetal membranes. Ghavi Hossein-Zadeh and Ardalan (13) demonstrated that cows with twins had a six times greater chance of developing metritis (OR: 6.5) and three times greater chance of developing a retained placenta (OR: 2.7) than cows with singletons (Table 2). Calculating the odds ratio using univariate conditional logistic regression, Potter et al. (12) found that twins were associated with clinical endometritis with an OR of 5 ($P = 0.003$). The birth of twins, dystocia, and the trauma associated with them enhance bacterial contamination of the uterus and increase the risk of developing a retained placenta, metritis, and clinical endometritis (20,37). However, Prunner et al. (10) found that twins were not significantly associated with clinical endometritis, although the small number of twin births in their study ($n = 18/400$) may explain the failure to demonstrate any relationship.

Markusfeld (19) reported a relationship between stillbirth and subsequent uterine infection and proposed that cows with stillbirths are often exposed to a retained placenta and metritis. Relative risk of stillbirth on the incidence of clinical endometritis was 3.1 according to Potter et al. (12) (Table 2). Indirectly, stillbirth increases the risk of clinical and subclinical endometritis by increasing the incidence of metritis with an OR of 6.3 (13). Placental immaturity associated with the shortened length of pregnancy seen in the case of stillbirth may also be part of the cause of a retained placenta, metritis, and endometritis (38).

2.2.4. Metritis

Until relatively recently, metritis and endometritis were not considered to be two separate clinical conditions (17,32). Currently, however, it would be inexcusable not to distinguish between these two uterine conditions (2,3). It is clear that almost all cows develop metritis without any systemic signs after parturition. There is then divergence: some cows return to normal while others develop puerperal metritis with systemic signs (3), and those cows that continue to have a contaminated uterus after the third week postpartum develop clinical or subclinical endometritis.

Cows that developed metritis soon after calving had a greater chance of developing clinical endometritis with an OR of 2.3 (20) (Table 2). Cheong et al. (7) confirmed this correlation and reported that metritis was a risk factor for subclinical endometritis with an OR of 1.9 (95% CI: 1.0–3.3). It seems that there is a positive correlation between the degree of the clinical signs of metritis and the risk of developing endometritis. Giuliadori et al. (30) worked on 303 dairy cattle and reported that cows that had puerperal metritis had a greater chance of developing

clinical endometritis than those that had clinical metritis (OR: 2.2 vs. 1.4, respectively). Since the relationship between metritis and endometritis appears strong, any risk factor that favors the development of metritis soon after calving may indirectly increase the risk of developing endometritis. Ghavi Hossein-Zadeh and Ardalan (13) found that dystocia (OR: 4.3), stillbirth (OR: 6.6), retained placenta (OR: 27.7), twins (OR: 6.6), primiparity (OR: 1.7), calving during winter (OR: 2.4), and male calves (OR: 2.4) significantly affected the risk of developing metritis.

2.2.5. Hypocalcemia

A failure of adequate calcium mobilization around the time of calving results in hypocalcemia. Since calcium is an important element in the process of uterine involution, any deficiency delays this process and is considered a risk factor for retained fetal membranes (OR: 3.6), and it may affect the incidence of metritis and endometritis (13) and the severity of endometritis (39).

Metabolic disorders including hypocalcemia may significantly affect the incidence of clinical endometritis (OR: 3.5, 95% CI: 1.1–10.8, $P = 0.03$) (11) (Table 2). Other authors confirmed that hypocalcemia reduces uterine contractions, causes dystocia, prolongs gestation, and increases the risk of occurrence of retained placenta and endometritis (40,41). Moreover, subclinical hypocalcemia decreases rumen motility, leading to reduced feed intake, which increases the risk of ketosis, and since hypocalcemia can affect rumen motility, it can indirectly increase the risk of developing a displaced abomasum (1,41). However, effects of a displaced abomasum on the incidence of endometritis are not yet well understood. Curtis et al. (42) and Markusfeld (43) reported a significant correlation between displaced abomasum and clinical endometritis with ORs of 3.6 and 4.7, respectively, but in these two studies it was not possible to distinguish between clinical endometritis and metritis (Table 2). Kim and Kang (11) examined the effect of metabolic disorders on the occurrence of clinical endometritis and concluded that metabolic disorders (displaced abomasum, hypocalcemia, ketosis) significantly increased the prevalence of clinical endometritis in dairy cows ($P < 0.03$). As these authors (11) included the three metabolic disorders within one variable, interpretation of the correlation between a displaced abomasum and clinical endometritis is difficult. Even if metabolic problems may significantly affect the occurrence of retained fetal membranes and this is considered as a risk factor that affects the incidence of endometritis, Cheong et al. (7) found that this correlation was not always significant.

2.2.6. Mastitis

Mastitis represents a source of bacterial contamination within the environment that may favor the development of endometritis. Often, isolated bacteria in the case of

uterine infections are nonspecific, often environmental bacteria that contaminate the uterus during parturition (4). Indirectly, the risk factors for mastitis are sometimes considered to be risk factors for endometritis. Among these factors are retained placenta (OR: 9.4), milk fever (OR: 12.4), multiparity (OR: 2.8), and calving during winter (OR: 1.7) (13). Subclinical mastitis can directly and significantly influence the prevalence of subclinical endometritis at 30 days postpartum and 60 days postpartum with ORs of 4.5 and 3.6, respectively (15). Even if the odds ratio of mastitis for the prevalence of clinical endometritis is higher than 1, sometimes the relationships are not statistically significant (12).

2.2.7. Negative energy balance

A negative energy balance (NEB) is often linked with severe and prolonged uterine inflammation and delayed uterine involution, which appear to be associated with a lack of bacterial killing after ingestion by phagocytes (44–46). NEB favors the development of many metabolic disorders, especially ketosis, which can increase the main important risk factors for endometritis, namely retained placenta and metritis, by 6.1 to 9.5 times (43). Subclinical ketosis was considered as a gateway condition for many metabolic disorders such as clinical ketosis and displaced abomasum, and infectious problems like metritis and mastitis (47). At the start of lactation, dairy cows require a significant amount of glucose to produce lactose, and these requirements are maximal after the third week of postpartum. During this period, dairy cows have insufficient appetite to consume the required energy. Energy deficiency results in lipid mobilization and ketone accumulation that can reach toxic concentrations and reduce immune functions and increase the risk of endometritis (33,48).

In vitro studies showed that high plasma ketone concentrations negatively and significantly reduced the efficiency of the ovine nonspecific immune system including phagocytosis and neutrophil chemotaxis (49). According to Kim and Kang (11), metabolic disorders including ketosis significantly affect the prevalence of clinical endometritis (Table 2). Cheong et al. (7), working on 779 dairy cattle, found that ketosis was a risk factor for subclinical endometritis with an OR of 3.8 (95% CI: 1.8–8.1).

Lipid mobilization induces an accumulation of nonesterified fatty acid (NEFA), which increases the potential for endometritis in 80% of cases and contributes directly to a strong inflammatory reaction by binding to Toll-like receptor 4 (TLR4) and starting an inflammatory cascade through TNF (25,50). Moreover, high postpartum NEFA levels increased the risk of clinical endometritis with an adjusted OR of 1.0 ($P < 0.05$) (30). The elevation of circulating plasma NEFA induces hepatic steatosis (fatty

liver) and impairs polymorphonuclear function, notably phagocytosis (46). The diminution of feed intake capacity, NEB, and lipid mobilization contribute actively to poor immune function from 2 weeks before calving to 3 weeks after calving (44).

High-yielding dairy cows are more exposed to the effects of the NEB and are more likely to develop endometritis (7,19). Since the postpartum period is characterized by low food ingestion capacity, NEB, and lipid mobilization, metabolic disorders and fatty liver are common and both reduce the efficiency of the immune system (44,48). Furthermore, the modification of anatomical, histological, and cytological properties of the genital tract challenges cows with a wide range of bacteria when the immune system is 'out of order' and prolonged endometritis can therefore develop.

According to Chaffaux et al. (29), high milk yield seems to reduce the prevalence of clinical endometritis, but Giuliodori et al. (30) found that cows with clinical endometritis had significantly higher milk production than cows without endometritis (27.8 ± 0.9 vs. 25.7 ± 0.4 kg/day, $P = 0.04$). For the subclinical form, Cheong et al. (7) reported that increasing milk yield increased the risk for subclinical endometritis in primiparous cows but lowered the risk in multiparous cows. We think that the prevalences of clinical and subclinical endometritis are not influenced by the milk yield of the cow, since endometritis and milk yield result from the interaction of many intrinsic and extrinsic factors such as age, breed, feed ration, general health, and body condition score (BCS).

Cows with very high or very low BCS may suffer prolonged pregnancy, dystocia, retained fetal membranes, persistent uterine infection, and endometritis (25,51). Kadivar et al. (52) showed that cows with clinical endometritis had significantly lower BCS than normal cows at all weeks before and after calving ($P < 0.05$). Moreover, the loss of 1 to 1.5 points of BCS between 30 days before calving to 30 days after calving was often associated with a high prevalence of clinical endometritis. This effect may have been associated with hepatic steatosis further to lipid mobilization (40,50). These observations were also confirmed for subclinical endometritis and it was found that cows with a low BCS (≤ 2.5) at 30 days postpartum had significantly higher prevalences of subclinical endometritis with an OR of 4.5 (15,16). Because NEB is inevitable around calving, to prevent a decrease of BCS many farmers increase the amount of concentrate fed, which increases the risk of acidosis (25). The fall of rumen pH favors the growth of pathogenic bacteria and the production of bacterial endotoxins like LPS that of course is occurring at the same time as the immune system is negatively affected by decreasing food intake (25,53).

2.2.8. Cyclicity

Clinical and subclinical endometritis are common causes of delayed resumption of ovarian activity after parturition, and importantly the onset time of the resumption of ovarian activity itself significantly affects the process of uterine involution and consequently the potential for the development of endometritis (31,54,55). Dairy cows that have early resumption of ovarian activity are less predisposed to endometritis at 30 days postpartum compared with cows that resume cyclicity later (31,54). In the case of endometritis induced by gram-negative bacteria such as *Escherichia coli*, the LPS inhibits the secretion of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) without affecting the secretion of follicle-stimulating hormone (FSH), but it also suppresses the sensitivity of the pituitary gland to GnRH (2). As a result, follicular waves develop but the dominant follicle does not ovulate, or when ovulation does occur, the resultant corpus luteum persists due to inadequate synthesis of uterine PGF₂α. In the latter case, the continuous secretion of progesterone delays the recruitment of phagocytic cells and the efficiency of the immune system is then decreased (2,54).

Thibier and Steffan (31) demonstrated that cyclic cows had less than 30% chance of developing metritis compared with less than 50% chance for noncyclic cows ($P < 0.01$). Delayed resumption of ovarian activity represents a risk factor for spontaneous recovery from uterine infection due to improved immune function (18) and phagocyte recruitment and function induced by estrogen. Furthermore, estrogen results in significant secretion of cervical mucus (18,56), which is considered to be a physical barrier that prevents bacterial entrance into the uterus. Interestingly, despite these observations, Sheldon

and Dobson (37) did not demonstrate a clear effect of ovarian cyclicity on the incidence of endometritis, possibly because of complications of NEB in the population of cows studied (45,57).

3. Conclusions

Endometritis is a multifactorial disease and determining its risk factors has great potential as a source of information that must be considered for the treatment and prevention of endometritis. Many risk factors and details about clinical and subclinical endometritis are as of yet unknown and only a few extrinsic risk factors such as calving season and nutrition and intrinsic factors such as parity, dystocia, retained placenta, metritis, hypocalcemia, mastitis, NEB, and cyclicity have been identified and studied. We have developed a concept map for endometritis that will be useful for researchers and educators (Figure). Within this review it was interesting, but not surprising, that there were interactions between the risk factors themselves; for example, a variety of nutritional imbalances, high or low BCS, and high milk yield may all predispose to endometritis. The prevalence and severity of endometritis are related to the condition of the livestock as extrinsic factors but also to intrinsic factors specific to each cow, which means that even in the same herd some cows may be more susceptible to developing and sustaining endometritis than other cows. For these reasons, for prevention and before treating affected cows, the most important risk factors must be identified and treatment should be adapted specifically to each cow according to the clinical examination of the intrinsic and extrinsic risk factors identified. This may result in better management of endometritis and thus will reduce the associated economic losses.

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