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Subclinical Endometritis in Dairy Cows: Related Risk Factors and Pre-partum Predictive Biomarkers

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Abstract

The aim of this work was to monitor the role of some risk factors on the incidence of endometritis in the herd, in addition to investigating the ability to make early pre-partum forecasting for occurrence of endometritis. 110 Holstein Friesian cows aged from 3-5 years were enrolled in this study. Cytological examination using a cytobrush (CB) and Indian MAP rapid stain kit (Indian MAP scientific©) for counting of polymorphonuclear cells (PMN) under microscope was used as the most accurate tool to discriminate between healthy cows and those affected with subclinical endometritis (SCE) at either 21 or 45 days postpartum (dpp). Serum analysis was used to measure the level of Albumin and Haptoglobin (Hp) in serum of dam at day 7 before parturition and at 21 and 45 dpp. Male calf and rainy season of parturition have a significant effect on the incidence of endometritis ($P < 0.05$). According to our study results, the prevalence of CE (N=15) is 16.48%, whereas that of SCE (N=34) is 37.36%. Albumin (a negative acute-phase protein) level has been discovered to be a trustworthy predictor of sickness risk in transition period and fresh cows. The standard range of Albumin in cow's serum is (2.8-3.9 g/dl). Albumin was markedly higher in healthy cows than diseased cows either prior to parturition or after 21 and 45 days in milk (DIM), The pre-partum Hp concentration between the SCE and healthy groups in this study was significantly different in a deceptive way. Hp concentration in the SCE group, however, was significantly different from the control group at 21 DIM (0.10±0.01 g/l vs. 0.05±0.002 g/l). So, Hp concentration is a satisfactory diagnostic, not a prognostic test.

KEYWORDS
Albumin, Cytology, Haptoglobin, Risk factors, Subclinical endometritis.

INTRODUCTION

One of the fundamental building blocks in the growth of a herd and an individual animal is reproductive health. Uterine diseases like endometritis and metritis, which have severe negative effects on an animal's productivity, can harm the reproductive health of female animals (Umer *et al*., 2022). Endometritis is characterized as endometrial-specific inflammation (Palmer, 2014). Uterine inflammation slows the process of involution in the uterus and delays the start of ovulatory activity, which results in economic loss from systemic disease, decreased milk and meat production, and a significant decline in fertility (Deori and Phookan, 2015). As a result, in order to have the least negative effect on the farms' profitability, it is essential to identify the risk factors and diagnose this pathology as soon as possible (Yáñez *et al*., 2022). There are two further subcategories of endometritis: clinical and subclinical disease (Palmer, 2014). Sheldon *et al*. (2006) reported that, in the absence of systemic symptoms of illness, clinical endometritis (CE) is the inflammation of the uterine endometrial lining followed by a purulent or mucopurulent vaginal discharge. Meanwhile, subclinical endometritis (SCE) is distinguished from clinical endometritis by the absence of purulent or mucopurulent uterine discharge in the vagina and is identified by the proportion of polymorphonuclear (PMN) cells in endometrial samples taken from cows at the beginning of the lactational phase. Despite the clinical difference between them, both problems manifest ≥21 days postpartum (Yáñez *et al*., 2022). In this sense, the innate immune system's ability to function is the primary component that guards against the development of uterine illnesses following calving. It has been established that endometrial cells express genes that code for a variety of aspects of the innate immune system activity more prominently during this time: Type Toll receptors, inflammatory mediators, and effector molecules (Sheldon *et al*., 2004; Chapwanya *et al*., 2009). Moreover, there is a significant influx of PMN. This intrinsic immunological capability in healthy animals can get rid of bacterial infection. As a result, the balance between the microorganisms that colonize the uterus, the animal's immune system, and the environment determines whether clinical indications appear (Potter *et al*., 2010). One of the most significant drivers of the development of uterine pathology among the many parameters is the energy state of the pre-partum animals (Manimaran *et al*., 2016). It is thought that

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hormonal and metabolic changes around parturition suppress the uterine defense mechanism, which encourages the development of uterine disease in dairy cows (Mateus *et al*., 2002; Kim *et al*., 2005). Postpartum uterine infection prevention and early treatment are more cost-effective than treatment once the disease has already taken hold. Thus, early detection or forecasting of uterine infections is crucial for efficient postpartum care. Finding a biomarker for early uterine infection prediction has been challenging because postpartum problems are multifactorial in nature (Manimaran *et al*., 2016). This study looked at the impact of several risk variables on the prevalence of endometritis in the herd and the feasibility of early pre-partum prediction for the development of endometritis.

MATERIALS AND METHODS

Ethical approval

The protocol of this study has been reviewed and approved by Zagazig University-Institutional animal care and use committee (ZU-IACUC) with approval number: ZU-IACUC/2/F/445/2022.

Experimental design

This study was performed at Dairy complex of West Nubariyah of Egyptian Armed Forces, Beheira Governorate, Egypt. During the period from September 2021 to October 2022. A total number of 110 Holstein Friesian cows aged 3-5 years and of different parities were enrolled in this study. All cows were housed outdoors in open hygienic yards, with free access to water, fed 3 times daily on total mixed ration (TMR) consisted of (corn silage, derris, concentrates and feed additives) according to (NRC, 2001), milked twice daily, mineral blocks containing essential supplementary minerals were available all the time, the farm was apparently free from infectious diseases and all animals were received the annual vaccinations. All cows were followed up from 1 week before parturition until 21 days and 45 days postpartum. The season of parturition, gender of the calf, and parity of the dam were recorded. Cows that suffered from a poor body condition score (BCS), mastitis, lameness, dystocia, retained placenta (RP), acute puerperal metritis, or unknown postpartum fever were subsequently excluded from the study.

Serum sampling and analysis

Coccygeal venipuncture was used to collect blood samples into centrifuge tubes without anticoagulant. Blood samples were collected on day 7 before parturition and on 21 and 45 days postpartum. Samples were centrifuged at 1500×g for 15 min. Aliquots of serum were kept at -20 °C until analysis (Bogado Pascottini and LeBlanc, 2020). A commercially available bovine Haptoglobin ELISA test kit was used to analyze Haptoglobin (Life Diagnostics, Inc.). All procedures were carried out in accordance with the manufacturer's instructions (Shin *et al*., 2018). At pH 4.1, albumin was evaluated using the bromocresol green reaction (Burke *et al*., 2010).

Cytological sampling

Cytological samples were collected at 21 and 45 days in milk (DIM). According to Kasimanickam *et al*. (2005), The traditional cytobrush handle was reduced in length to around 3 cm, threaded onto a 65 cm solid stainless-steel rod, and then inserted into a 50 cm long, 5 mm diameter stainless steel tube for cervix passage. The tool was encased in a clean plastic sleeve to prevent vaginal contamination. Cleansing the vulva with wet paper towels was followed by passing the covered, lubricated instrument through the vagina to the external cervical os. The sanitary sleeve was then punctured, and the instrument was then advanced through the cervix into the base of the larger horn. At this point, the stainless-steel tube was retracted enough to reveal the cytobrush. By turning the cytobrush clockwise while it was in contact with the uterine wall, endometrial cytology samples were obtained. Before being taken out of the uterus, the cytobrush was withdrawn into the stainless-steel tube. Between uses, the stainless-steel tool was steam sterilized for 4 minutes. Glass slides were instantly prepared by rolling the cytobrush over them. Then slides treated with Indian MAP rapid stain kit (Indian MAP scientific©) that consists of 3 solutions: Methanol, Eosin and Azor. Staining was conducted according to the instructions of the manufacturer. To offer a quantitative evaluation of endometrial inflammation, cytological examination measured the percent neutrophils (% PMN) by counting a minimum of 100 cells at 400x magnification under microscope (Kasimanickam *et al*., 2004). (Madoz *et al*., 2013) stated that the percentage of PMN with subclinical endometritis was given a cutoff value of 5%.

Statistical Analysis

It was performed using the Statistical Package for Social Sciences (SPSS) version 22.0. Chi-square test was used for testing incidence of endometritis in relation to gender of newborn, season, and parity of cows. Results of Albumin and Haptoglobin and PMN% are represented in Mean±SE and tested using Duncan's test and Paired sample t-test respectively. Values P <0.05 was considered to be significant.

RESULTS

Clinical endometritis was distinguished from SCE by presence of purulent vaginal discharge (PVD) of different scores at 21 DIM. Our study revealed that the prevalence of CE (n.=15) is 16.48% against 37.36% for SCE (n.=34). Healthy cows were distinguished from SCE group by counting PMN%. Healthy cows represent the control group (n.=42 with a percentage of 46.15%). Plus, excluding 19 cows for the previously mentioned causes.

In Table 1, PMN% was significantly different (P <0.05) between subclinical endometritis and control groups after 21 and 45 DIM. In contrast, within subclinical endometritis group or control group themselves, there was no significant difference (P > 0.05) at 21 nor 45 DIM.

Table 1. Percentage of polymorphonuclear cells in different groups.

Groups	N	After 21 dpp	After 45 dpp	P-value
Subclinical endometritis	34	7.57±0.96	6.14±0.73	0.07
Control	42	3.80±0.29	3.61±0.31	0.7
P-value		< 0.00	< 0.00	

Data are expressed as Means ± SE. P < 0.05 means significant difference

At P <0.05 in Table 2, there was a significant difference between groups of endometritis in relation to sex of calf. Male calves contributed to 26.09, 34.78 and 39.13% for clinical, subclinical endometritis and control groups respectively. Meanwhile, female calves contributed to 6.67, 40, 53.33% for clinical, subclinical endometritis and control groups respectively.

In Table 3, there was a significant difference (P <0.05) between groups of endometritis in relation to season of parturition.

In winter, the incidence was 22.39, 41.79, 35.82% for clinical, subclinical endometritis and control groups respectively. But in summer, incidence was 0, 25, 75% for clinical, subclinical endometritis and control groups respectively.

Table 2. Incidence of endometritis in relation to gender of newborn.

Calf sex	N	Clinical endometritis	Subclinical endometritis	Control
Male	46	12 (26.09%)	16 (34.78%)	18 (39.13%)
Female	45	3 (6.67%)	18 (40.00%)	24 (53.33%)
P-value			0.04	

P < 0.05 means significant difference

Table 3. Incidence of endometritis in relation to season

Season	N	Clinical endometritis	Subclinical endometritis	Control
Winter	67	15 (22.39%)	28 (41.79%)	24 (35.82%)
Summer	24	0 (0.00%)	6 (25.00%)	18 (75.00%)
P-value			0.02	

P < 0.05 means significant difference

In Table 4, there was no significant difference (P > 0.05) between groups of endometritis in relation to parity of cows.

Table 4. Incidence of endometritis in relation to parity

Parity	N	Clinical endometritis	Subclinical endometritis	Control
Primiparous	42	6 (14.29%)	18 (42.86%)	18 (42.86%)
Multiparous	49	9 (18.37%)	16 (32.65%)	24 (48.98%)
P-value			0.6	

P < 0.05 means significant difference

Regarding to Albumin results, as demonstrated in Table 5, there was a significant difference (P <0.05) between subclinical endometritis and control group at each stage of the study. On the other hand, when comparing Albumin values within diseased or healthy cows themselves through the study. In subclinical endometritis group, Albumin concentration was significantly varied between before parturition and 45 DIM stage, but at 21 DIM, there was no significance difference (P > 0.05) between either before parturition or 45 DIM stage.

Table 5. Albumin (g/dl) level in different groups.

Groups	N	Before parturition	After 21 dpp	After 45 dpp
Subclinical endometritis	34	2.07 ± 0.03^{a}	2.37 ± 0.14^{ab}	2.62 ± 0.09^{b}
Control	42	3.04 ± 0.03^{a}	2.71 ± 0.11^{b}	3.11 ± 0.04^{a}
P-value		< 0.00	< 0.00	< 0.00

Data are expressed as Means ± SE. The different superscript letter within rows means significant difference at P < 0.05.

Hp concentration, as shown in Table 6, was significantly varied (P <0.05) between diseased and control groups during the stage of before parturition and 21 DIM, but at 45 DIM there was no significant difference (P > 0.05). Meanwhile, within subclinical endometritis group, Hp was significantly higher at 21 DIM than stage of before parturition, but at 45 DIM there was no significant difference. In control group, Hp at 45 DIM was significantly different from its concentration during 21 DIM and before parturition.

Table 6. Haptoglobin (g/l) level in different groups.

Groups	N	Before parturition	After 21 dpp	After 45 dpp
Subclinical endometritis	34	0.07 ± 0.01^{a}	0.10 ± 0.01^{b}	0.08 ± 0.01^{ab}
Control	42	0.06 ± 0.002^{a}	0.05 ± 0.002^{a}	0.07 ± 0.004^{b}
P-value		< 0.00	< 0.00	0.11

Data are expressed as Means ± SE. The different superscript letter within rows means significant difference at P < 0.05.

DISCUSSION

Based on Sheldon *et al*. (2006), in this study, clinical endometritis (CE) cases had been recognized by presence of PVD on 21 DIM. Hence, other cows without PVD are supposed to be healthy or SCE cases which is a fundamental need to differentiate between them. Asfar *et al*. (2021) reported that the best minimally invasive diagnostic technique for the identification of SCE is endometrial cytology using CB. At cutoff value of 5% PMN, data in table 1 showed that SCE cows recorded PMN% exceeding 5% at both 21 and 45 DIM, and control group recorded a ratio lower than 5% with a significant difference between the two groups. This result is confirmed by Madoz *et al*. (2013). Also, Gabler *et al*. (2009) and Fischer *et al*. (2010) reported that, cows having an endometrial sample that had ≥ 5% PMN had a dysregulated cytokine and prostaglandin profile, which supports the idea that using 5% PMN as a diagnostic cutoff for subclinical endometritis.

In our field study, we tried to link between incidence of endometritis and some of incriminated risk factors. Our findings confirmed that incidence of clinical endometritis is associated with delivery of male calf more than female calf. This fact is consisted with Potter *et al*. (2010) and Pascal *et al*. (2021). The physical harm, human involvement, and pollution of the cow's reproductive system just before calving may be blamed for the obtained findings (Sheldon *et al*., 2009). These data prompt us to propose that sire selection, sexed semen, and the care of cattle during parturition, rather than their hygiene, should be the primary considerations in the design of uterine disease control strategies (Potter *et al*., 2010).

Regarding the season of parturition, incidence of CE and SCE was related to cold weather more than hot one. The association between these two factors may be explained by the fact that cows' general health declines during the wet seasons, leaving them more susceptible to uterine infections (Bruun *et al*., 2002). Other researchers, on the other hand, discovered that the calving season had no effect on either clinical (Kim and Kang, 2003) or subclinical endometritis (Carneiro *et al*., 2014). These discrepant findings can be attributed to the fact that diagnostic standards and climatic conditions varied throughout investigations, particularly the average environmental temperature, which varied greatly between the locations where the experimental activities were undertaken (Adnane *et al*., 2017).

In the present study, there was no significant relationship between parity of cow and incidence of endometritis. In fact, this result is discordant with Bruun *et al*. (2002) who reported that heifers are more vulnerable to endometritis than second parity cows because uterine injury is more common in heifers, and third parity cows are more sensitive to endometritis than second parity cows because the uterus takes longer to involute and there is a higher risk of infection, and with Pascal *et al*. (2021) who confirmed that there were more SCE cases linked to higher cow parity, which may be explained by the multiparous cows' cumulative exposure to uterine bacterial contamination over time due to unsanitary farmers' calving aid intervention. This conflict can be interpreted as in our study we excluded all cows that had an abnormal parturition or that required major calving assistance. Also, the herd under study is relatively younger than those in other studies, providing less parities, hence, a less cumulative effect on uterine health, elasticity, and involution capacity.

During inflammation, plasma proteins like Albumin serve as transporters for the movement of molecules like fatty acids (Mazzaferro *et al*., 2002) and Haptoglobin is produced as response to pro-inflammatory cytokines into blood stream (Chan *et al*., 2010).

In close-up and fresh cows, the Albumin level has been found to be a reliable indicator of illness risk (Van Saun, 2004). In healthy cows, the usual range for Albumin levels is 2.8-3.9 g/dl (Kahn and Line, 2010). The obtained results reported that in pre-partum stage, Albumin concentration in control group was 3.04±0.03 g/dl which is significantly higher than (2.07±0.03 g/dl) in SCE group. Bobe *et al*. (2004) reported that lower Albumin can be an indicator of fatty liver infiltration, which is a known risk factor for uterine disorders. Burke *et al*. (2010) and Schneider *et al*. (2013) assessed serum Albumin as a marker of liver function and found that in cows later found to have uterine illness (endometritis), Albumin levels were lower prior to delivery. On the other hand, after delivery, it is noticeable from our findings that a shared decrease in Albumin concentration is present at 21 DIM within both control and SCE groups. Meanwhile at 45 DIM, the attitude of Albumin concentration is shifting toward increase again reaching the normal level (3.11±0.04 g/dl) in control group against (2.62±0.09 g/dl) for SCE group, keeping the significant difference between them at ($P < 0.05$). Our outcomes are consistent with results of Burke *et al*. (2010); Bogado Pascottini and LeBlanc (2020) and Yáñez *et al*. (2022). Role of Albumin in this issue have been clarified by Bobe *et al*. (2004); Valergakis *et al*. (2011) and Arfuso *et al*. (2016) who reported that near and after calving, most dairy cows experience a negative energy balance (NEB) status, and the concentrations of non-esterified fatty acid (NEFA) and ketone bodies significantly rise. The triglycerides kept in adipose tissue undergo lipolysis during NEB, producing glycerol and NEFA. The latter are non-covalently linked to serum Albumin and enter the circulation. Therefore, changes in Albumin levels could result in unbound NEFA and its storage as triglycerides in the liver, which could develop fatty liver and worsen NEB.

In response to uterine infection brought on by microbes, APPs are created in the liver, and their concentration in the blood serum of cows rises throughout the first few weeks following delivery (Sheldon *et al*., 2001, Tóthová *et al*., 2008). Huzzey *et al*. (2011) discovered that pre-partum cows that experienced several disorders or died within 30 days of producing milk tended to have higher HP concentrations. Whereas in healthy cows, only low blood levels of Hp and SAA can be found (Chan *et al*., 2004). In this study, a significant difference in Hp concentration was recorded between SCE (0.07±0.01 g/l) and healthy (0.06±0.002 g/l) groups in pre-partum stage. In fact, regardless of the difference, this result is tricky to discuss. Because of the narrow difference and the very low value of Hp detected making us doubtful to depend on it as prognostic tool for endometritis. Huzzey *et al*. (2015) assessed the relationship between pre-partum Hp and milk production and reproductive efficiency. They discovered a poor correlation between Hp and milk production and reproductive efficiency, which weakened the credibility of Hp as pre-partum prognostic tool. But at 21 DIM, there was a significant difference between Hp concentration in SCE group (0.10±0.01 g/l) and control one (0.05±0.002 g/l). And as time goes on, Hp concentration at 45 DIM in SCE group is declined till reach low value (0.08±0.01 g/l) with no significance difference between it and control group (0.07±0.004 g/l), this result is to some extent agreed with Ricci *et al*. (2017) who discovered that, at either 30 or 60 DIM, there was no difference in the serum Hp concentration between animals with negative or positive cytology or bacteriology. So, Hp can be used as benefit diagnostic tool up to 21 DIM. Many authors confirmed our finding, such as study of Bogado Pascottini and LeBlanc (2020) who reported that in the first two weeks following delivery, cows with PVD or SCE at 35 DIM, have higher serum Hp concentrations than healthy cows, implying higher inflammation prior to illness. These findings suggest that a high serum Hp concentration in the postpartum period is related to a higher incidence of pre- and postpartum problems, even if the Hp concentrations measured in each of the groups are inconsistent between studies (Shin *et al*., 2018).

CONCLUSION

Albumin measurement is outstanding easy and applicable test to make accurate prediction about animal energy status and subsequently, subclinical endometritis. Hp is a poor prognostic tool and needs more investigations, but good diagnostic one especially in early weeks postpartum.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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