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**Sheldon, IM. (2018) Metabolic stress and endometritis in dairy cattle. *Veterinary Record* 183, 124-125. First published July 27, 2018.**

### **Metabolic stress and endometritis in dairy cattle**

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Endometritis is a significant condition in postpartum dairy cattle because it causes infertility.<sup>1</sup> Although pathogenic bacteria underlie the aetiology of clinical endometritis (see Box 1 for definitions), peripartum problems such as dystocia and retained placenta increase the risk of disease. Metabolic stress is another risk factor for clinical endometritis,<sup>2; 3</sup> and a recent study by Valdmann and others, published in the *Veterinary Record*,<sup>4</sup> extends this observation to include cytological endometritis. This finding is important because metabolic stress is a common feature of intensive dairy farming, and metabolic demands on cows will rise further because milk yields are expected to double in the next 50 years.<sup>5</sup>

#### **Box 1. Definitions for postpartum uterine diseases**

**Metritis:** an enlarged uterus and a watery red-brown fluid to viscous off-white purulent uterine discharge, within 21 days and usually within 10 days of parturition.

**Clinical endometritis:** the presence of a purulent uterine discharge detectable in the vagina 21 days or more post partum.

**Cytological endometritis:** the percentage of neutrophils exceeding a threshold, usually between 5 and 18% of cells, in endometrial cytology samples collected 21 days or more post partum.

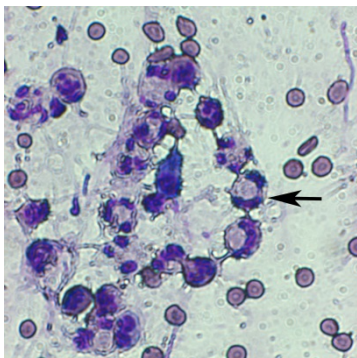
**Subclinical endometritis:** the percentage of neutrophils exceeding a threshold, usually between 5 and 18% of cells, in endometrial cytology samples collected 21 days or more post partum, in the absence of pus detectable in the vagina.

### **Metabolic stress is associated with endometritis**

In the first 3 weeks after calving, the inflammatory process helps the endometrium remodel itself and resist bacterial infections. Cytological endometritis is the persistence of this inflammation beyond 3 weeks post partum. Diagnosing cytological endometritis relies on measuring the proportion of neutrophils in cytobrush samples collected from the uterus (Fig. 1).<sup>6</sup> Valdmann and others used > 8% neutrophils at 40 days post partum as the threshold for the diagnosis of cytological endometritis.<sup>4</sup> Thirty per cent of the cows in their study had cytological endometritis, and these animals took longer to conceive and more were culled, compared with normal animals. As expected, cytological endometritis was associated with periparturient problems, including twins, retained placenta, metritis, and clinical endometritis. However, the most interesting finding was that markers of metabolic stress were also risk factors for cytological endometritis.

Insulin-like growth factor-1 (IGF-1) is a widely studied hormone that regulates metabolism. Low blood concentrations of IGF-1 reflect negative energy balance in peripartum cows, and are associated with uterine disease and infertility.<sup>2; 3</sup> Valdmann and others found that cows with low concentrations of IGF-1 in blood samples collected two weeks before or one week

after parturition, were also 3.5 to 4.4 times more likely to develop cytological endometritis than cows with normal IGF-1 concentrations.<sup>4</sup> These findings are timely because there is emerging evidence that immunity and cell metabolism are highly integrated, and that metabolic stress impairs immunity.<sup>7</sup> Although the reduced availability of IGF-1 might compromise immune cell function directly, the low IGF-1 concentrations in blood could alternatively be a marker of metabolic stress and other mechanisms may be at work in the endometrium. For example, limiting the availability of glucose or glutamine, but not IGF-1, impairs the ability to mount inflammatory responses to pathogens in endometrial organ cultures.<sup>8,9</sup>



**Figure 1.** Cytological endometritis is characterised by the presence of polymorphonuclear neutrophils (arrow) in uterine cytology preparations.

### **The transition period is crucial**

The most striking feature of the recent paper was that low IGF-1 concentrations in blood two weeks before calving were associated with cytological endometritis 40 days after calving.<sup>4</sup> Furthermore, thin cows two weeks before calving, with a body condition score < 2.75, were 6.8 times more likely to develop cytological endometritis than cows in body condition score 3.5 to 3.75. Clearly, it is important to feed cows before drying off to ensure they have an appropriate body condition during the transition period. However, we still need a better understanding about how dry cow and transition cow diets can help animals cope with the postpartum period.

### **Endometritis presents challenges for veterinarians**

The current method for diagnosis of cytological endometritis is inconvenient because it relies on the laboratory examination of uterine cytobrush samples. There is also little agreement about when the samples should be collected during the postpartum period, and the proportion of neutrophils to use as a threshold to diagnose endometritis.<sup>6</sup> Consequently, there is an urgent need for a rapid, accurate, and cost-effective cow-side method for the diagnosis of cytological endometritis.

Unfortunately, cytological endometritis does not discriminate between cows with a concurrent purulent uterine discharge and cows with subclinical endometritis. Furthermore, cows with subclinical endometritis have often previously had metritis or clinical endometritis. This lack of precision makes it difficult to disentangle the mechanisms that link uterine disease, metabolism, and fertility.

Another dilemma is how to manage cows with endometritis. The current treatments for clinical endometritis are to use prostaglandin  $F_{2\alpha}$  to induce oestrus, or infuse antimicrobials or antiseptics into the uterine lumen. Unfortunately, although these treatments help resolve the clinical signs they have little effect on subsequent fertility, and so selecting treatments for subclinical disease is even more speculative. What is clear is that animals with endometritis

are less fertile than normal animals, and so prevention is better than cure. Preventing endometritis will require new approaches such as nutraceuticals, vaccines, or immunotherapies. However, in the short-term, veterinarians can advise farmers about the nutritional and health management of cows during the transition period and early lactation to reduce the impact of metabolic stress and periparturient problems on endometrial health.

In conclusion, the association between metabolic stress and endometritis is important at a practical level for veterinarians (see Box 2). The challenge now is to find the mechanisms linking metabolism and endometritis, and to develop strategies to limit the risk of disease. In the long-term, genetic selection of robust animals may provide a solution to the challenge of sustainable intensification of dairy farming, whilst maintaining happy and healthy postpartum cows.<sup>5</sup>

#### **Box 2. Key information for veterinarians**

- Diagnosis of cytological endometritis relies on measuring the proportion of polymorphonuclear neutrophils in cytobrush samples collected from the uterus.
- Cytological endometritis affects about 30% of dairy cows 40 days post partum, and reduces fertility.
- Periparturient problems such as twins, dystocia, retained placenta, and metritis increase the risk of cytological endometritis.
- Thin cows or low blood IGF-1 concentrations, even 2 weeks before calving, increase the risk of cytological endometritis.
- Aim to dry cows off at body condition score 3 to 3.75, and maintain this condition during the transition period to reduce the risk of endometritis.
- Aim to minimize metabolic stress and particularly negative energy balance in early lactation to support dairy cow fertility.

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