Mastitis and the link to infertility

Mastitis and infertility are the two most common disease complexes in dairy cattle worldwide. Both are major reasons for culling and have profound negative effects on the profitability of a farm, writes Lucy Metcalfe BVSc DipECEIM GCertVPM MRCVS

For many years, dairy producers and their advisers have recognised the detrimental effects of mastitis on performance mainly because of its impact on animal welfare and milk production occurring at the time of the clinical event. It is now clear, however, that mastitis cases can have an influence on the long-term future of the cow and her productivity by affecting her ability to become pregnant and remain in the herd. This article discusses the link between mastitis and fertility in order to help maximise the future welfare and longevity of dairy cows.

THE EFFECT OF MASTITIS ON FERTILITY

The impact of mastitis on dairy fertility has previously been established through a number of trials; however, numerous factors could have been confounding the assessment of the relationship. For example, higher-yielding cows are commonly considered to be at higher risk of mastitis but also tend to have poorer fertility. More recent work has further examined the effect of the type of mastitis, the degree of elevation of somatic cell count (SCC), the timing of the mastitis incident and the type of pathogen using statistical techniques which take account of these confounding relationships.

TYPE OF MASTITIS

Mastitis is generally classified as clinical or subclinical, depending on the degree of inflammation in the mammary gland. While subclinical mastitis is defined by elevation of the SCC beyond a certain cut-off point (ie. 200,000 cells/ml), clinical mastitis is characterised by visible abnormalities of the milk (eg. watery milk, flakes, clots) and udder (eg. swelling and hardness of the affected quarter, pain).

Several studies have demonstrated considerable negative effects of clinical mastitis on days to first insemination (up to 22 days more) and days to conception (up to 44 days more). Furthermore, clinical mastitis can alter the inter-oestrous interval, making oestrous detection more difficult.

More interestingly, an elevation of SCC, typical for subclinical mastitis, around artificial insemination (AI) is also associated with a significant reduction in probability of conception. Around 30% of cows with subclinical chronic mastitis have delayed ovulation, low concentrations of oestradiol and a low or delayed pre-ovulatory surge of luteinising hormone. In one study, subclinical mastitis followed by clinical mastitis resulted in the most severe loss in reproductive performance. Considering the nature of subclinical mastitis (not obvious and only detectable by testing or screening), the high prevalence (up to 40%) and the multitude of effects, these relationships require attention both in the field and in research.

PATHOGEN EFFECT

Different types of clinical mastitis (ie. different causal pathogens) may have varying effects on reproduction. One classification method for clinical mastitis is by staining the causal pathogens into gram-positive and gram-negative. Clinical signs, severity and treatment protocols differ for gram-positive and gram-negative mastitis. Older studies did not find any differences between gram-positive and gram-negative clinical mastitis in their effect on reproduction. More recently, however, there is evidence that clinical mastitis caused by gram-negative pathogens is associated with larger

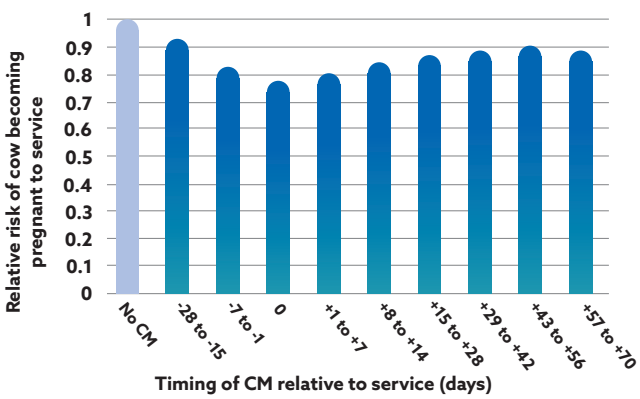

Figure 1: Association between clinical mastitis in a variety of timeframes relative to insemination, and probability (risk) of the cow becoming pregnant to that serve. Error bars show area of 95% highest posterior density (analogous to confidence interval).

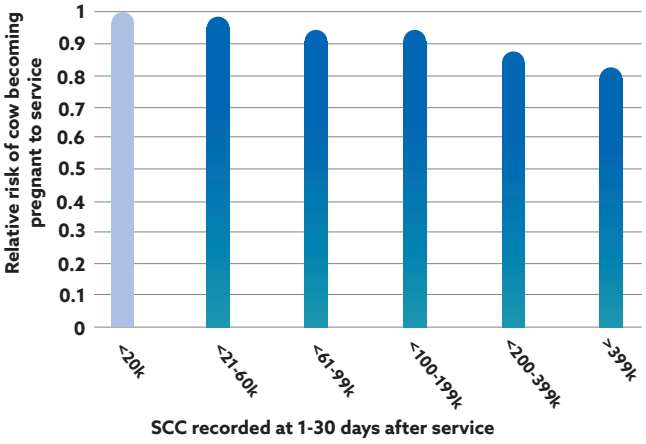

Figure 2: Association between individual cow SCC at 1-30 days after insemination and the probability (risk) of pregnancy resulting from the service. Error bars show area of 95% highest posterior density (analogous to confidence interval).

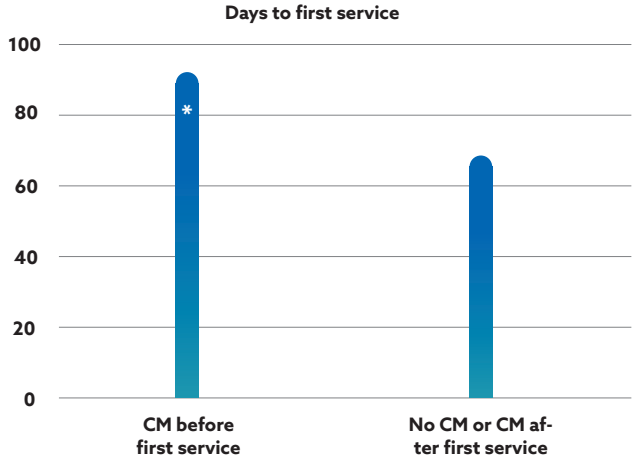

Figure 3: Cows with clinical mastitis (CM) before first service had a longer interval between calving and first service (93.6 days) than cows with CM after first service or no CM at all (71 days) (* P <0.01).

decreases in probability of pregnancy compared to that caused by gram-positive pathogens.

A retrospective analysis based on 23,695 lactations found that clinical mastitis due to gram-negative bacteria had a more detrimental effect on probability of conception than did clinical mastitis caused by gram-positive bacteria or other organisms. The greatest effect was an 80% reduction in probability of conception associated with gram-negative clinical mastitis occurring in the week after AI.

TIMING OF MASTITIS RELATIVE TO INSEMINATION

It is well documented that the negative effect of mastitis on fertility varies with the timing of mastitis occurrence relative to AI.

A recent UK study used data from 105 dairy herds, including a total of 85,482 inseminations.[1] The associations found between clinical mastitis and the outcomes of a serve are shown in Figure 1.

Clinical mastitis occurring at the time of insemination was associated with a reduction in conception rate of almost 25%, and mastitis within a week of insemination associated with a reduction of around 20%. Mastitis in all timeframes studied up to but not beyond 70 days after insemination had a smaller but significant association with the outcome of the serve (as measured by subsequent calving).

LARGER EFFECT WITH HIGHER CELL COUNT

A negative association between SCC and conception rate was also demonstrated (Figure 2). A SCC reading of 400,000 or higher, within the 30 days after an insemination, was

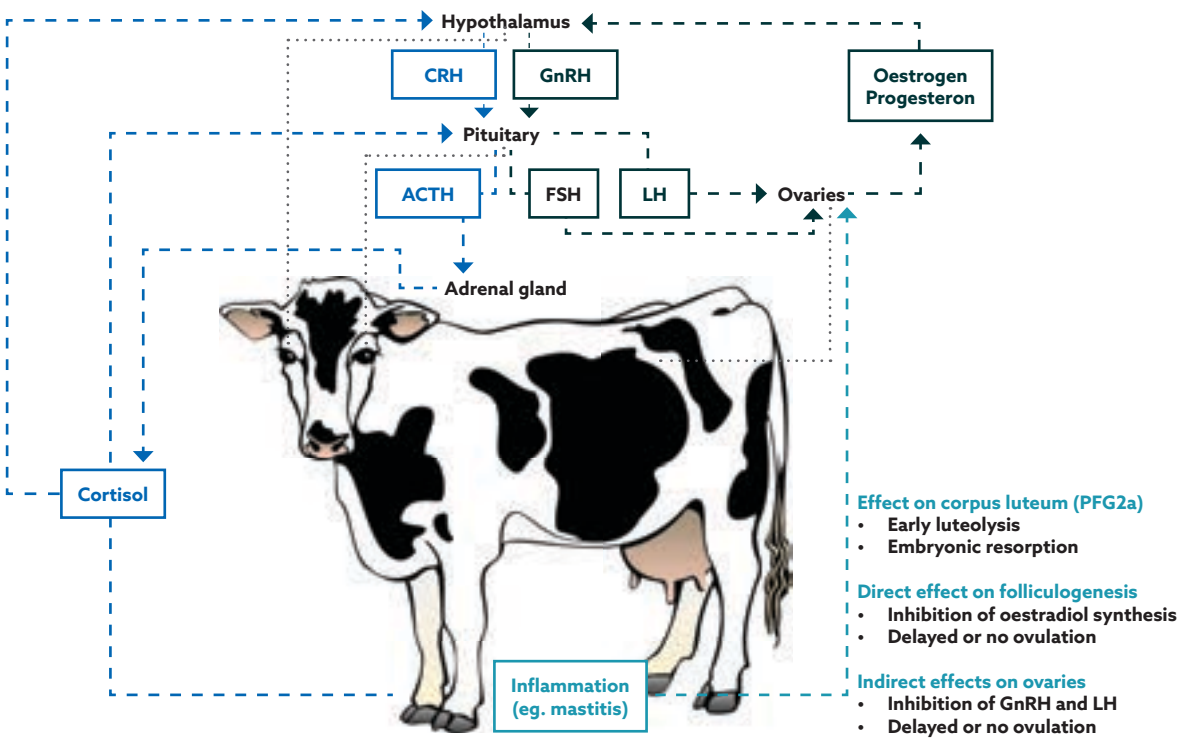

Figure 4.

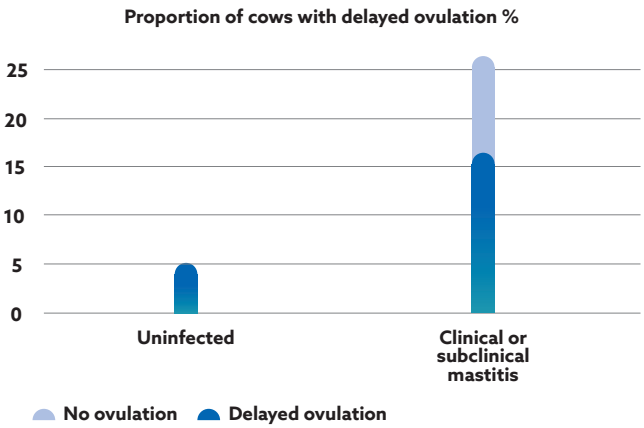

Figure 5: The proportion of cows that experienced a delay in ovulation after onset of oestrous in both uninfected and mastitis cows.

associated with a reduction of almost 20% in the probability of the serve leading to a pregnancy. Smaller effect sizes were seen with lower SCC readings, but all categories were significantly different to the 'reference' category.
Furthermore, the effects of SCC on conception rate were additive with those of clinical mastitis: a cow with clinical mastitis at the time of insemination plus a SCC >400,000 within the next 30 days would have a predicted reduction of around 45% in the probability of pregnancy resulting from that serve.
This study found that both clinical mastitis and elevated SCC could influence the probability of a cow being served, as well as the probability of a given serve leading to pregnancy. This could be due to either an effect of mastitis on the ovulation itself or the level of oestrous behaviour expressed by the cow. Alternatively, it could simply reflect farmers avoiding inseminating cows which they knew recently had mastitis.
In summary, recent studies have revealed that larger reductions in conception rate were associated with mastitis occurring at, or shortly after, insemination, and where the causal organism was gram negative. In addition, SCC has an additive effect with clinical mastitis, with higher cell counts associated with larger reductions in conception rate.

MECHANISMS OF THE EFFECT OF MASTITIS ON FERTILITY

The precise mechanisms by which intra-mammary infections, and resultant inflammation, affect conception or maintenance of pregnancy are yet to be fully elucidated. There are a number of proposed pathways, likely exerting their effects at different stages of the reproductive cycle, which illustrate the important impact of inflammation on fertility.

EARLY LUTEOLYSIS

When a bacterial pathogen induces inflammation of the mammary gland, inflammatory mediators (prostacyclines, thromboxane A and prostaglandins) are produced. Inflammation increases the permeability of local blood vessels in the udder; PGF2a is likely absorbed into the circulation and reaches the ovaries. If an active corpus luteum is in place, early luteolysis may be induced. This impairs embryo implantation or causes resorption due to a decline in progesterone levels and increased contractility of the uterine smooth muscle.
Several papers confirm this theory, with one study reporting that cows with clinical mastitis after ovulation had a higher proportion of short luteal phases.[2] In fact, the developing ovarian follicle has been shown to be able to respond to the presence of bacterial infection regardless of the source or site of infection within the body.
However this 'early luteolysis' theory fails to explain why cows with clinical mastitis have increased days to first service, as shown in Figure 3.[3]

THE HYPOTHALAMIC-PITUITARY AXIS

Studies on the effect of endometritis provided new insights into the impact of inflammation on hormonal balance. Endotoxins led to the production of cortisol, a strong inhibitor of the hypothalamic-pituitary axis (Figure 4). Cortisol decreases the GnRH pulse amplitude in the hypothalamus, which has an immediate effect on the basal LH pulse amplitude in the pituitary gland.
The decrease in basal LH concentrations inhibits follicle growth with, as a consequence, lower pre-ovulatory oestradiol concentrations. This means the cow will either not have an oestrus or will not express it well enough. She will also fail to generate an effective LH surge, which means that ovulation will be blocked or delayed. Some follicles will not ovulate but form cysts instead.[4]

DIRECT EFFECT ON THE FOLLICLE

The above mechanisms do not explain why both clinical and subclinical mastitis events can influence a cow's subsequent fertility (eg. the association between serve outcome and a mastitis event in the preceding weeks).
Recent works include a study with 73 cows synchronised for insemination.[5] In the mastitis group (clinical and subclinical cases), 26% of cows showed delayed ovulation and some never ovulated in the 96-hour study period (Figure 5). All cows in the mastitis group had normal basal LH pulses, which means the hypothalamus or pituitary gland were not involved. However, the oestradiol concentrations were significantly lower in cows with delayed ovulation.
These results can be explained by a direct suppression of follicular oestradiol production. The mechanism behind this suppression is not yet clear, but cytokines are likely to play a role.

DIRECT EFFECT ON THE OOCYTE

Not only the follicle, but also its enclosed oocyte, is highly sensitive to inflammation. The oocyte can be affected indirectly by hormonal imbalances, such as described above; correct oestradiol concentrations are required for maturation, while perfect timing of the LH surge is crucial for the success of conception. But inflammation can also have a direct effect on the oocyte. Short-term in vitro exposure of oocytes to endotoxins or pro-inflammatory cytokines was found to disrupt oocyte maturation and subsequent embryonic development.[6]

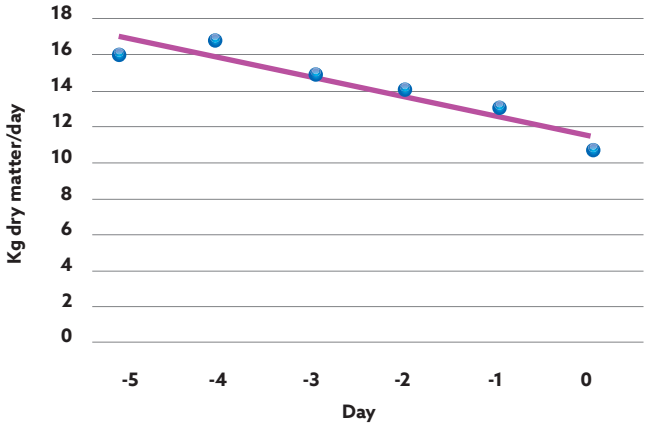

Figure 6: Cows reduce their feed intake five days prior to diagnosis of a moderate case of mastitis.

SICKNESS BEHAVIOUR DURING MASTITIS

Early lactation is the most challenging period for the cow's metabolism, in addition to being the period with the highest incidence of mastitis. Behavioural changes during illnesses such as mastitis aim to conserve energy, increasing the effectiveness of the immune system. However, conserving energy by reducing appetite undoubtedly adds pressure to the negative energy balance that a cow experiences during the transition period, inevitably affecting her subsequent fertility. This mechanism, and the effect of negative energy balance on fertility, will be discussed further in the following section.

In summary, the fertility of the dairy cow is influenced by both disease and inflammation occurring at sites in the body distant to the ovary. The mechanism of the effect of mastitis is dependent on the timing of the mastitis incident but all pathways illustrate the extensive impact of inflammation on fertility. The reduction of inflammation should therefore be seen as an important part of enhancing the reproductive performance in cows.

THE EFFECT OF NEGATIVE ENERGY BALANCE ON FERTILITY

Negative energy balance and excessive loss of body condition are frequently reported as causes of poor reproductive performance. It is generally accepted that negative energy balance, just like inflammation, can hamper the well-orchestrated process of follicular growth.[7] The pathogenesis of this sub-fertility syndrome is complex. A disturbance of the hypothalamic-pituitary-ovarian-uterine axis causes endocrine signalling to be impaired. This leads to a delayed resumption of ovarian cycling post-partum. Biochemical parameters such as non-esterified fatty acids (NEFA), associated with a negative energy status, can reach the follicular fluid and reduce the oocyte's ability to develop. Furthermore, insulin and glucose concentrations are

decreased during the period of negative energy balance early post-partum. Insulin not only promotes the response to gonadotropins, and thus follicular growth, but probably also has a direct stimulatory effect on the maturing oocyte. Insulin and insulin-like growth factor are major regulators of granulosa cell proliferation and oestrogen synthesis. Low insulin results in peripheral lipolysis in the cow, and elevated concentrations of NEFA which, in turn, have a detrimental effect on granulosa cell function.[8]

MASTITIS INCREASES NEGATIVE ENERGY BALANCE

In managing the transition period, good-quality feed is important, but the appetite of the cow is vital; disease or pain affects appetite. Increased negative energy balance may partially explain why mastitis can have an effect on fertility, even when it occurred long before ovulation and first service. On the one hand, pain-induced behaviour may cause deterioration in the metabolic condition and hence prolong the post-partum anoestric phase. On the other hand, it is known that oocytes can be damaged by an early episode of negative energy balance.

Primary follicles have thin walls, exposing the enclosed oocyte to close contact with the blood. During the 80-day-long follicular growing phase, the oocyte grows more isolated and protected, yet the hormonal and biochemical environment still defines the follicular capacity to produce steroids and to deliver a perfect oocyte.

WELFARE IMPLICATIONS OF MASTITIS

Sickness behaviour is well recognised in severe mastitis, yet farmers may be less aware that such changes also occur in moderate cases, when only milk and one or more quarters are affected, without the presence of fever.

In fact, researchers have shown that cows with moderate mastitis decreased their feed intake from five days before the mastitis case was diagnosed (Figure 6).[8] This may not be noticed by farmers as it was a reduction in feeding rate rather than feeding time.

UDDER PAIN CAUSES BEHAVIOURAL CHANGES INCLUDING A REDUCTION IN APPETITE

It is likely that pain in the udder contributes to the animals' unwillingness to move, and thus walk to the feeder. Clearly, cows with mastitis visit the feeder less often than their healthy herd mates but, when at the feeder, they also eat more slowly. This strongly suggests that, just as in humans, pain reduces the cows' motivation to eat. Furthermore, there seems to be a state of pain-induced depression. Pain clearly affects the social behaviour of cows and the position which a cow takes in the herd hierarchy; a painful or depressed cow is likely to be replaced at the feeder by other cows. This explains why cows with moderate mastitis eat less during peak feeding times, when competition for a feeding place is highest.[9]

MASTITIS REDUCES FERTILITY WHICH RESULTS IN INCREASED CULLING RATES

Studies have shown that infertility is the greatest reason for culling.[10] McDougall et al showed that by adding the non-steroidal anti-inflammatory drug (NSAID) meloxicam to an antibiotic mastitis treatment, fewer treated cows were culled when compared with a control group.[11] The hypothesis was that, by reducing the inflammation of the mastitis, the cows became pregnant more easily and were, therefore, more likely to be kept for the next lactation.

CONCLUSION

The described effects of mastitis on fertility reinforce the need for health and treatment protocols that not only prevent subclinical disease but also provide effective cures that remedy not just the clinical signs of disease but also the subclinical consequences. There is a convincing body of evidence associating mastitis with impairment of different aspects of the reproductive process in dairy cows. These effects are relatively large; dairy farmers should therefore be reminded to work to reduce clinical mastitis incidence rates, as well as rates of subclinical infection. However, no mastitis control regime is perfect, and measures to mitigate the effects of mastitis on reproductive performance would be useful. The high economic value of generating a pregnancy means that even a small reduction in the influence of mastitis on fertility could lead to a net benefit.

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