TECHNICAL BULLETIN

Part 2
A happy cow is a productive cow

Inflammation and fertility: Recent research demonstrates long term benefits of a one-off treatment of METACAM[1,2,3]

Mastitis, lameness, and infertility are common disease complexes in dairy practice. All are multifactorial, major reasons for culling and have significant negative impacts on farm profitability.

Mastitis pain and inflammation has significant negative implications for animal health as well as production.[1,2] The negative effects of inflammation associated with lameness have also been shown to increase the probability of future lameness, chance of culling and negatively impact reproduction in dairy cows.[3,4]

Studies by McDougall *et al.*[1,2] and Mason and Laidlaw[3] demonstrated the addition of a single treatment of METACAM 20 mg/mL Solution for Injection to the standard treatment of mastitis or lameness, significantly improved the reproductive performance of dairy cows in New Zealand.

Whilst a well-regulated acute inflammatory response may be necessary for normal bovine reproductive physiology and the housekeeping aspects of the reproductive processes, excessive or chronic inflammation, whether local or systemic, adversely affects fertility, oocyte quality, and embryonic development.[5,6]

This technical bulletin discusses the concept of 'productive wellbeing' and the potential mechanics behind the link between inflammation caused by mastitis and lameness with respect to fertility.

How does inflammation impact reproduction?

Whilst a certain level of controlled, acute inflammation (e.g., presence of polymorphonuclear neutrophils at AI) may be beneficial to fertility, likely by supporting uterine defence and tissue remodelling,[5,6] the link between inflammatory conditions such as mastitis and reduced fertility has been evident for some years.[7,8] Recent findings published in the Journal of Dairy Science indicated that treating cows with METACAM for claw horn lameness can also lead to improvements in reproductive outcomes, including conception rate, six-week-in-calf rate (6WICR), and final pregnancy rate.[3]

While in the case of mastitis and lameness, the adverse effects of inflammation on reproduction may initially be attributed to behavioural changes such as reduced feeding and rumination times, (leading to negative energy balance), and mobility impairments that hinder oestrus expression and detection,[9] we will explore and discuss additional factors potentially involved in the relationship between these inflammatory conditions in dairy cows and their reproductive efficiency.

The role of PGF2α

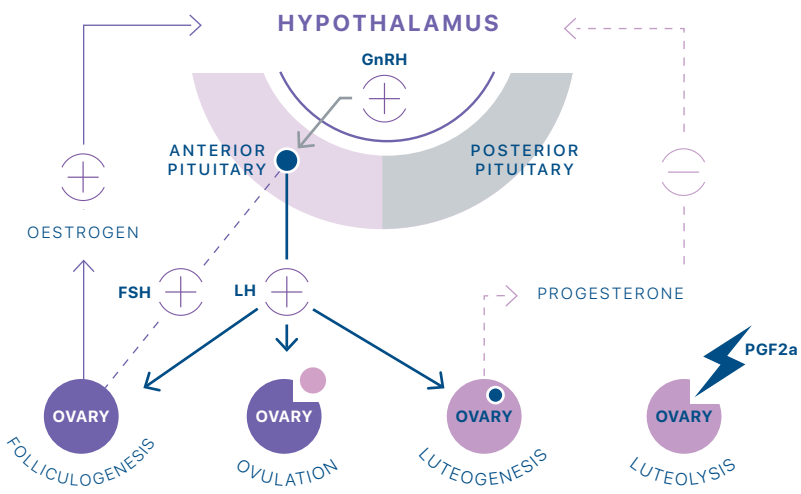
PGF2α is a naturally occurring prostaglandin which causes luteolysis of the corpus luteum (CL). Within the inflammatory cascade, there is production of proinflammatory mediators such as prostacyclins, thromboxane A and prostaglandins, including PGF2α.[1,2] Inflammation also increases the permeability of local blood vessels. Therefore, the PGF2α is likely to be absorbed systemically and reach the ovaries. When the production of PGF2α as part of the inflammatory cascade coincides with an active CL, any ensuing early luteolysis and subsequent loss in progesterone may lead to early embryonic resorption and loss of pregnancy.[7,10,11]

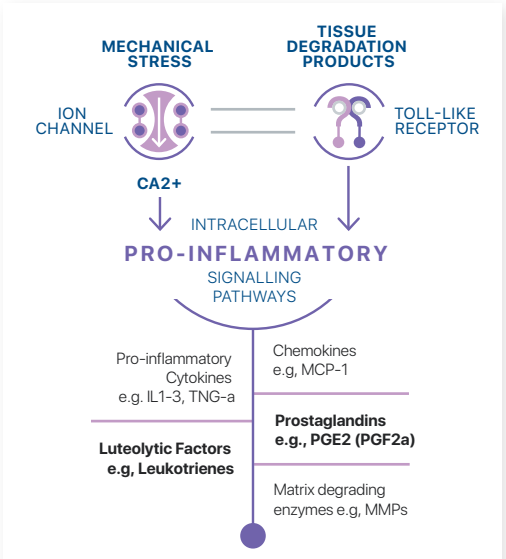
However, whilst the early luteolysis theory may in part explain embryo loss, it does not fully account for inflammation impacting other aspects such as conception rates.[7]

The hypothalamus-pituitary axis

The reproductive process in dairy cows is regulated by a complex cascade of combined activities involving the central nervous system (CNS), several secretory tissues, target tissues and many hormones. The hypothalamus-pituitary axis is responsible for the interplay between the CNS and gonads in the control of female reproductive function both producing hormones and acting as target organs for homeostatic feedback systems (Figure 1). Gonadotropin releasing hormone, (GnRH), initiates the release of follicle stimulating (FSH) and luteinising hormone, (LH), from the pituitary gland which is in turn responsible for development of the follicle and the formation of the CL after ovulation. Oestrogens are secreted by the ovary in response to FSH, driving oestrus behaviour and providing a positive feedback loop to the hypothalamus. After ovulation, progesterone is the primary gonadotropin released by the developing CL. Progesterone has a negative effect on the hypothalamus and has pro-gestational effects on the uterus.[12]

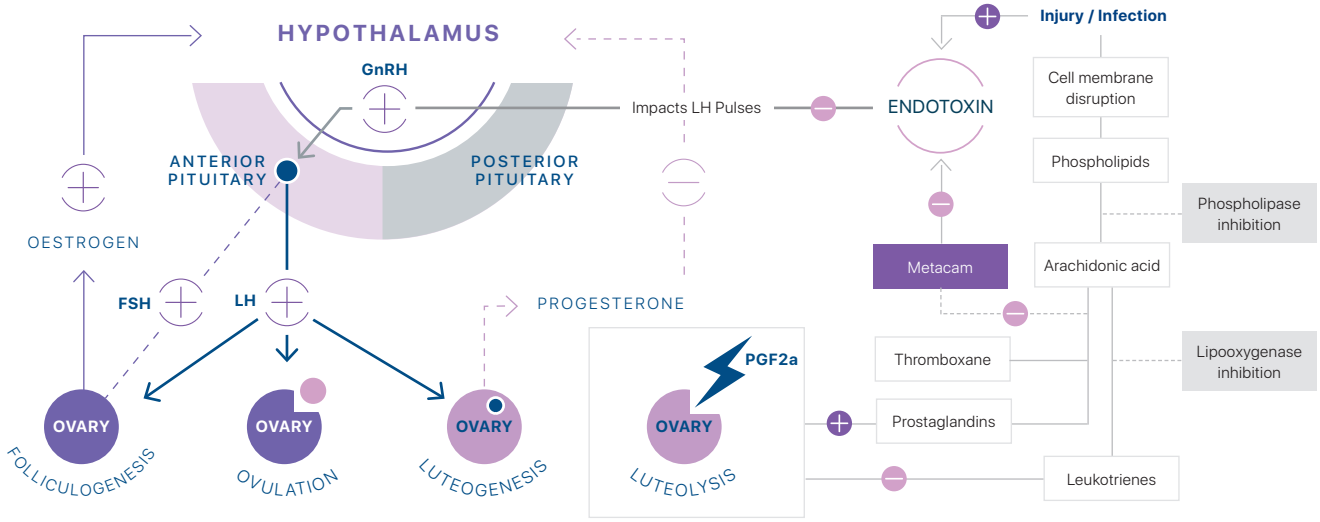
Figure 1





Normally each GnRH pulse generates an LH pulse, but in the presence of endotoxemia, this is no longer the case. LH pulse frequency is affected, but not GnRH, suggesting that inflammation has a direct effect on both the hypothalamus and the pituitary. Lower basal LH concentrations inhibit follicle growth and therefore pre-ovulatory oestradiol concentrations. This results in either anoestrus or reduced expression of oestrus behaviours and the absence of an LH surge. The result is ovulation is either delayed or arrested with the potential for cysts to develop on the ovary.[13] (Figure 2). Cortisol is released as part of the stress response as well as the release of endotoxins in certain infectious inflammatory conditions. Cortisol has a negative feedback effect on the hypothalamus, resulting in the decoupling of GNRH and LH pulses.[9] This work is based on experimental models and may not be representative of the long-term effects at a follicular level.

Figure 2



Direct effects on ovarian structure, follicle or oocyte

Cows with chronic mastitis showed reduced ovarian vascularity, increased fibrotic tissue, and lower levels of GDF-9, (growth and differentiation factor-9).[14] These negative effects on folliculogenesis could also partly explain the detrimental effect of mastitis on dairy cow fertility. In a 2010 study, 26% of cows with mastitis showed delayed or absent ovulation despite normal basal LH levels.[15]

This suggests that the hypothalamus or pituitary was not involved despite concurrent oestradiol levels being significantly lower in the affected cows. These results suggest direct suppression of follicular oestradiol production may also be involved in the reduction in reproductive efficiency associated with the inflammatory cascade.

In addition to direct effects on the follicle, the enclosed oocyte is extremely sensitive to inflammation and hormonal imbalances as previously described.

For example, the correct concentration of oestradiol is required for nuclear maturation, and perfect timing of the LH surge is critical for the success of conception. Add in the direct effects observed in a short term in-vitro study exposing oocytes to inflammatory cytokines or endotoxin and the subsequent disruption of oocyte maturation and embryonic development,[16] one is left with a feeling that the interplay between inflammatory conditions, (mastitis, lameness) and fertility is vastly oversimplified.

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Whatever the underlying cause, reproductive efficiency, which is critical to dairy farm profitability, is negatively affected by inflammatory conditions such a mastitis and lameness.[3,4,8,17] Therefore, effective management of the medium to long-term deleterious effects of inflammation, appears crucial for optimising reproductive outcomes in dairy cows.

A systematic review by Mason *et al.*[18] found that there was little evidence that NSAIDs, improved lameness cure risk without appropriate trimming and the use of blocks. However, in a recent randomised controlled trial Mason and Laidlaw found that despite the addition of meloxicam to the treatment of cows with claw horn lameness not reducing the time to soundness in dairy cows, it did significantly improve their reproductive outcomes.[4] These outcomes throw into question the subjective nature of lameness score to measure welfare benefits of NSAIDs given the improvement in conception, 6WICR and final pregnancy rate with a single injection of METACAM added to standard treatments, and call into question the appropriate choice of NSAID for treating dairy cows with lameness.

The authors suggest that this improvement may be due to METACAM's anti-inflammatory effects, which may reduce the negative impact of lameness on reproductive performance.

In the case of lameness or mastitis, whether this is due solely to the factors discussed above or also extends to improved cow comfort contributing to increased mobility and ability to reproduce, there is now compelling evidence to recommend METACAM for the major economic inflammatory conditions in cattle, (mastitis and lameness).

1. McDougall S, *et al.* Effect of treatment with the nonsteroidal antiinflammatory meloxicam on milk production, somatic cell count, probability of re-treatment, and culling of dairy cows with mild clinical mastitis. J Dairy Sci. 2009;92(9):4421-31. 2. McDougall S, *et al.* Addition of meloxicam to the treatment of clinical mastitis improves subsequent reproductive performance. J Dairy Sci. 2016;99(3):2026-42. 3. Mason WA, *et al.* The effect of meloxicam at the time of treatment of hoof-horn lameness in pasture-grazing dairy cattle on time to lameness soundness, pregnancy risk, and time to conception: A randomized control trial. J Dairy Sci. 2025;108(4):3991-4004. 4. Wilson J. P, *et al.* 2022. Effects of routine treatment with nonsteroidal anti-inflammatory drugs at calving and when lame on the future probability of lameness and culling in dairy cows: A randomized controlled trial. J. Dairy Sci. 105(7):6041-6054. 5. Aurich, C., Drillich, M., Wagener, K., & Gabler, C. 2021. Endometrial Inflammation at the time of insemination and Its effect on subsequent fertility of Dairy Cows. Animals : an Open Access Journal from MDPI, 11. https://doi.org/10.3390/ani11071858. 6. Chastant, S., & Saint-Dizier, M. (2019). Inflammation: friend or foe of bovine reproduction?. Animal Reproduction, 16, 539 - 547. 7. Barker AR, *et al.* Influence of clinical mastitis during early lactation on reproductive performance of Jersey cows. J Dairy Sci. 1998;81(5):1285-90. 8. Schrick FN, et al. Influence of subclinical mastitis during early lactation on reproductive parameters. J Dairy Sci. 2001;84(6):1407-12. 9. Tsousis, G., Boscos, C., & Praxitelous, A. 2022. The negative impact of lameness on dairy cow reproduction. Reproduction in Domestic Animals, 57(Suppl. 4), 33–39. 10. Giri SN, *et al.*, Effects of endotoxin infusion on circulating levels of eicosanoids, progesterone, cortisol, glucose and lactic acid, and abortion in pregnant cows. Veterinary Microbiology, 1990; 21(3):211-231. 11. Moore DA, *et al.* Evaluation of factors that affect embryonic loss in dairy cattle. J Am Vet Med Assoc. 2005; 226(7):1112-8. 12. Intervet International. Compendium of animal reproduction. 8th Revised edition, 2003, pp 2-12. 13. Lavon Y *et al.* Naturally occurring mastitis effects on timing of ovulation, steroid and gonadotrophic hormone concentrations, and follicular and luteal growth in cows. J Dairy Sci. 2010;93(3):911-921. 14. Rahman MM, *et al.* Chronic mastitis is associated with altered ovarian follicle development in dairy cattle. J Dairy Sci. 2012;95(4):1885-93. 15. Cook J. The influence of metritis and mastitis on dairy herd fertility: some case examples. UK vet. 2010; 15(6):38-40. 16. Roth Z, *et al.* Naturally occurring mastitis disrupts developmental competence of bovine oocytes. J Dairy Sci. 2013;96(10):6499-6505. 17. Fuenzalida MJ, *et al.* The association between occurrence and severity of subclinical and clinical mastitis on pregnancies per artificial insemination at first service of Holstein cows. J Dairy Sci. 2015;98(6):3791-805. 18. Mason, W., *et al.* Graduate Student Literature Review: A systematic review on the associations between nonsteroidal anti-inflammatory drug use at the time of diagnosis and treatment of claw horn lameness in dairy cattle and lameness scores, algometer readings, and lying times. J. Dairy Sci. 2022;105(11):9021-9037.

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