Does intrauterine cephapirin improve subsequent fertility in cows with clinical endometritis?

Bobby Hyde, Marnie Brennan

BOTTOM LINE

- The evidence suggests that cephapirin improves subsequent fertility in dairy cows affected by clinical endometritis when compared with no treatment.

Clinical scenario
During a routine fertility visit, you find many cows with a white vaginal discharge 21 to 28 days after calving, and you discuss with the farmer the implications of endometritis. After discussing preventative measures for endometritis and examining the farm’s transition cow management, the farmer tells you that, when your boss does the routine visit, he puts Metricure tubes (MSD Animal Health) (an intrauterine treatment containing 500 mg cephapirin) in to ‘wash the cows out and get them in calf quicker’. You do not often use Metricure tubes, and you wonder whether there is any evidence behind using intrauterine cephapirin to improve reproductive outcomes.

The question
In [dairy cows with clinical endometritis] does [the use of cephapirin versus nothing] improve [subsequent fertility]?

Search parameters
The search strategy can be viewed at https://bestbetsforvets.org/bet/561, and it is also available as a supplement to this article on Vet Record's website at https://veterinaryrecord.bmj.com/content/186/11/350

Search outcome
- Eighty papers were found in the Medline search.
- Sixty-nine were excluded because they did not answer the question.
- Five papers were excluded as they were not available in English.
- In total, four relevant papers were obtained.
- Three hundred and ten papers were found in the CAB search.
- Two hundred and ninety were excluded because they did not answer the question.
- Twenty papers were excluded as they were not available in English.
- In total, four relevant papers were obtained.
- Overall, a total of five relevant papers were identified.

Search last performed: 5 February 2020

One systematic review was found, but not all the papers within the review were relevant to the question. Therefore, the relevant papers were analysed separately. A Vet Record paper reporting the findings from the first time this search was run was also excluded from the analysis.

Summary of evidence

Paper 1: The effect of treatment of clinical endometritis on reproductive performance in dairy cows

- **Patient group:** A total of 316 Holstein cows from 27 herds, diagnosed with endometritis (ie, having purulent vaginal discharge or a cervical diameter of greater than 7.5 cm) between 20 and 33 days in milk, were examined.
- **Study type:** Randomised controlled trial.
- **Outcomes:** Clinical cure (ie, the absence of mucopurulent discharge and a cervical diameter of less than 7.5 cm) after 14 days, pregnancy rate, calving to service interval, likelihood of pregnancy after first service, calving to pregnancy interval, cumulative pregnancy risk, the number of inseminations per pregnancy, removal risk for reproductive failure and culling data were assessed.
- **Key results:** No significant differences in clinical cure after 14 days between treatment and control were seen. No significant effect of treatment on time to pregnancy or on pregnancy rate when given between 20 and 26 days in milk was seen. However, there was a significant effect of treatment on pregnancy rate (63 per cent increase, P=0.01) when cows were treated between 27 and 33 days in milk, and on pregnancy when a palpable corpus luteum was present (75 per cent increase, P=0.003).

Study weaknesses: The sample size was too small to detect small differences in reproductive outcomes, and not all animals underwent follow-up examinations. Blinding was not possible and ethical approval was not stated. Also, the study was funded by the company that manufactures the treatment, which could have led the study to be subject to bias.

Paper 2: Effect of intrauterine treatment with cephapirin on the reproductive performance of seasonally calving dairy cows at risk of endometritis following periparturient disease

- **Patient group:** A total of 222 dairy cows from 17 seasonally calving herds, with purulent vaginal discharge at 28 to 37 days before the mating start date.
- **Study type:** Randomised controlled trial.
- **Outcomes:** The hazard ratio for pregnancy was assessed.
- **Key results:** The chance of pregnancy occurring in treated discharge-positive cows was 2.09-fold (P=0.013) compared with control cows.

Study weaknesses: The study population consisted of animals that were at risk of endometritis (ie, those with dystocia or that had given birth to twins), which is a very specific group of animals and may not be representative of herd-level endometritis diagnosis in practice.

Cows were examined and treated at a variety of times after calving, frequently within the first 21 days in milk. Also, a large portion of the study was dedicated to analysis of data involving ‘at risk’ cows rather than those with endometritis, limiting the relevance of this study to the question being investigated here.

While the funding source was not stated, the company that manufactures the product provided product support for the study, which could have introduced an element of bias.

Paper 3: Comparison of two methods of detecting purulent vaginal discharge in postpartum dairy cows and effect of intrauterine cephapirin on reproductive performance

- Eighty papers were found in the Medline search.
- Sixty-nine were excluded because they did not answer the question.
- Twenty papers were excluded as they were not available in English.
- In total, four relevant papers were obtained.
- Overall, a total of five relevant papers were identified.
Patient group: A total of 261 dairy cows from six seasonal dairy herds were examined between seven and 28 days after calving and were found to have purulent vaginal discharge (diagnosed using either a Metricheck device or visual vaginoscopic examination).

Study type: Randomised controlled trial.

Outcomes: The proportion of cows conceiving at first service, the proportion of cows submitted for service within three weeks of the mating start date, the proportion of cows pregnant within six weeks of the mating start date, and the proportion of cows pregnant within 21 weeks of the mating start date were assessed.

Key results: The proportion of cows conceiving at first service was significantly higher in the treated group than in the non-treated group for cows diagnosed with endometritis by vaginal examination (P=0.036), but not for those diagnosed by Metricheck (P=0.15).

The proportion of cows serviced within three weeks of the mating start date was not statistically different between the treated group and non-treated group for cows diagnosed with endometritis by either method. (P=0.3).

The proportion of cows pregnant within six weeks of the mating start date was significantly higher in the treated group than in the non-treated group for cows diagnosed with endometritis by vaginal examination (P=0.015) and those diagnosed by Metricheck (P=0.011).

The proportion of cows pregnant within 21 weeks of the mating start date was significantly higher in the treated group than in the non-treated group for cows diagnosed with endometritis by vaginal examination (P=0.026), but not for those diagnosed by Metricheck (P=0.082).

Study weaknesses: As in the previous paper by Runciman and colleagues, the study population consisted of animals at risk of endometritis (ie, those with dystocia or that had given birth to twins), and so may not be representative of herd-level endometritis diagnosis in practice.

Animals were examined and treated as early as seven days after calving and, although a positive effect of treatment was reported, it is an earlier diagnosis and treatment than commonly seen in UK practice.

It was unclear if blinding was performed. Also, the required sample size was not reached, the funding source was not stated and basic data were not fully described. In addition, the outcome of interest for the purposes of this analysis was not the primary aim of the study.

Paper 6: Randomised clinical trial of intrauterine cephapirin infusion in dairy cows for the treatment of purulent vaginal discharge and cytological endometritis.

Patient group: Four hundred and twenty-four Holstein cows from 28 dairy herds within 250 km of Saint-Hyacinthe, Québec, with purulent vaginal discharge at 35 (± seven) days in milk.

Study type: Randomised controlled trial.

Outcomes: Pregnancy rate at first service was assessed.

Key results: Treatment with intrauterine cephapirin increased pregnancy rate at first service (31.3 per cent) compared with untreated controls (15.5 per cent) (P<0.01). A greater improvement in pregnancy rate at first service was seen in cyclic cows (treated cows 34.1 per cent; untreated cows 22.7 per cent) than anovular cows (treated cows 26.4 per cent; untreated cows 21 per cent).

Study weaknesses: Ethical approval for the study was not mentioned. There were some discrepancies between the figures in the text and in the tables (eg, the number of animals with purulent vaginal discharge), and there was a high culling rate before pregnancy diagnosis. In addition, the study was part-funded by the company that manufactures the treatment, so it may have been subject to bias.

Paper 5: Effectiveness of intrauterine treatment with cephapirin in dairy cows with purulent vaginal discharge.

Patient group: A total of 1247 dairy cows from 18 Canadian farms. All cows were enrolled in a presynch-ovsynch protocol.

Study type: Randomised controlled trial.

Outcomes: The odds of cows conceiving at first service, calving to pregnancy interval (up to 300 days in milk), the presence of vaginal discharge and bacterial cultures obtained from vaginal cytobrush were assessed.

Key results: Cephapirin treatment increased the odds of cows conceiving at first service (odds ratio=1.8, 95 per cent confidence interval 1.2–4.2, P=0.001) compared with untreated cows. Cephapirin treatment also reduced the calving to pregnancy interval compared with untreated cows (P=0.02), reducing the median time to pregnancy by 38 days.

Study weaknesses: The study used a convenience sample of Canadian cows, so the findings may not be representative of the wider dairy cow population. It was also unclear if blinding was performed.

Almost one-sixth of the cows (n=255) were removed from the study, primarily because they were not inseminated at the end of the synchronisation protocol (n=156). However, 70 cows were excluded from a single herd because of failure to follow the synchronisation procedure, which is likely to have an impact on the results from that herd.

Comments
There was a wide variety of methods used for the diagnosis of clinical endometritis within these studies. Additionally, the time periods between calving and diagnosis of, and treatments for, purulent vaginal discharge were very variable between the studies. This variability may or may not be relevant to local systems.

Both papers by Runciman and colleagues use an ‘at risk’ population of animals from which to draw a proportion diagnosed as having vaginal discharge. This is different from diagnosing endometritis directly from the whole herd, as occurred in the other studies evaluated.

Additionally, within these two studies, the cows were examined/treated at various times after calving – as early as seven days postpartum – which is again different from the other studies evaluated. This has the potential to affect the relevance of these two studies to specific types of clinical approach, particularly those where cows are not usually examined for clinical endometritis until after 21 days after calving.
While cephapirin appears to be effective at improving fertility in animals with clinical endometritis, it is important to consider the judicious use of antibiotics within farm animal practice.

Bobby Hyde, School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington, UK

Marnie Brennan, Centre for Evidence-based Veterinary Medicine, University of Nottingham, Sutton Bonington, UK
doi: 10.1136/vr.m1049

This is an updated version of a clinical decision making article originally published in Vet Record in April 2017.

References
1. Lefebvre RC, Stock AE. Therapeutic efficiency of antibiotics and prostaglandin F2α in postpartum dairy cows with clinical endometritis: an evidence-based evaluation. Vet Clin North Am Food Anim Pract 2012;28:79–96
2. Hyde B, Brennan M. Effect of intrauterine cephapirin on subsequent fertility in cows with clinical endometritis. Vet Rec 2017; doi: 10.1136/vr.j1635
3. LeBlanc SJ, Duffield TF, Leslie KE, et al. The effect of treatment of clinical endometritis on reproductive performance in dairy cows. J Dairy Sci 2002;85:2237–49
4. Runciman DJ, Anderson GA, Malmo J, et al. Effect of intrauterine treatment with cephapirin on the reproductive performance of seasonally cycling dairy cows at risk of endometritis following periparturient disease. Aust Vet J 2008;86:250–8
5. Runciman DJ, Anderson GA, Malmo J. Comparison of two methods of detecting purulent vaginal discharge in postpartum dairy cows and effect of intrauterine cephapirin on reproductive performance. Aust Vet J 2009;87:369–78
6. Denis-Robichaud J, Dubuc J. Randomised clinical trial of intrauterine cephalothin infusion in dairy cows for the treatment of purulent vaginal discharge and cytological endometritis. J Dairy Sci 2015;98:6856–64
7. Tison N, Bouchard E, DesCôtesaux I, et al. Effectiveness of intrauterine treatment with cephapirin in dairy cows with purulent vaginal discharge. Theriogenology 2017;89:305–17

CRITICALLY APPRAISED TOPICS (CATS) are a standardised, succinct summary of research evidence organised around a clinical question, and a form of evidence synthesis used in the practice of evidence-based medicine (EBM) and evidence-based veterinary medicine (EBVM). Access to CATs enables clinicians to incorporate evidence from the scientific literature into clinical practice. CATs will be published regularly in the Clinical Decision Making section of Vet Record.