Infuse, or not to infuse? That is the question.
A review on dairy cattle clinical endometritis and uterine infusion

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At the 15th International Congress on Animal Reproduction (2004), the research field concluded the need for a true definition of endometritis in order to conduct more parallel investigations.

*IM. Sheldo et al., 2006.

†Fonseca et al., 1983.
*Considered risk factors for uterine disease as they overwhelm the immune system’s ability to clear infection; unfortunately are not directly-related to environmental conditions (Grohn and Rajala-Schultz, 2000; Kim and Kang, 2002; Noakes et al. 2001). **Sheldon et al., 2009.
Debate over if the incidence is truly increasing, or if more attention has been paid to this condition in recent years and it is therefore more commonly diagnosed. Though the scope of this presentation is clinical endometritis, subclinical is on the rise and in the order of magnitude 37-74% (Gilber et al. 2005; Lincke et al. 2007).
Biological Consequences

- Infection causes:
  - Decreased growth of Graafian follicle
  - Especially in the presence of *E. coli*®
  - Lower peripheral estrogen and progesterone
  - LPS infused theca cells secrete less estrogen
  - LPS encourages progesterone, though cell survival diminishes
  - Ovulation failures

- Inflamed environment decreases trophectoderm cells surrounding embryo§
  - Reduces uterine implantation ability

- LPS presence–induced conversion of PGF2α to PGE
  - In ruminants, former is luteolytic, latter is luteotropic†

- Uterine periglandular fibrosis‡ and salpingitis
  - Latter, 16% in slaughtered animalsφ

**Williams et al. 2007.
*Herath et al. 2007.
*Grant et al. 2007.
§Hill and Gilbert, 2008.
†Poyser 1995; Arosh et al. 2004; Goravanahally et al. 2007.
φGonzalez et al., 1985.
Management Consequences

- Decreased conception rates*
  - Approximately 20% lower
  - Fresh to pregnant interval 30 days longer
  - 3% increased cull rate for fertility-related issues

*Borsberry and Dobson, 1989; LeBlanc et al. 2002
Intervention

- Antimicrobial
  - Widely held belief that direct administration limits systemic absorption and provides greater concentration
- Hormonal
  - Induce estrus; increase uterine tone; encourage drainage
- Benign neglect
  - Natural estrus cycles
Antimicrobials*: Antibiotic Considerations

- Anaerobic populations
  - Aminoglycosides relatively ineffective

- Organic debris
  - Sulfonamides are inactivated

- Presumed penicillinase production by the mixed population of lochia
  - Penicillins are ineffective

This was taken from Bretzlaff’s article “Rationale for treatment of endometritis in the diary cow” featured in the 1987 edition of Veterinary Clinics of North America, Food Animal Practice, Bovine Reproduction. As this publication is popular among private-practice veterinarians, I made the assumption that its content was well read and formed the basis, and encouraged the popularity therein, of intrauterine treatment for endometritis of the 1990’s.
Antimicrobials*: Antibiotic Considerations cont

- Oxytetracycline considered drug of choice
  - Can be administered intrauterine, broad-spectrum, effective in debris and low oxygen tension
    - Bacteriostatic
    - Plasma: uterine greatly decrease post partum
      - Basis of intrauterine infusion

- Clinical metritis (systemic clinical signs) warrant systemic administration
Antimicrobials*: Nonantibiotic Considerations

› “Dilution is the solution to pollution”

› Irritating effect
  ◦ Stimulate uterine tone, mucus production, blood flow, and increase immune function
  • Few controlled studies to support claims
  • Physiologic saline would have similar, albeit less irritating, effects

› Chlorhexidine is only approved intrauterine infusion product

*Same as previous slide.
In particular, uterine infusion of chlorhexidine was widely viewed as non-adverse considering it was not considered an antibiotic and therefore had no withdrawal time. Regardless of scientific inquiry into its success, producers often viewed it as satisfying their desire for risk aversion; similar to the proverb “Something is better than nothing.”
While the author described that, due to the differences in treatment, no placebo could be established. I disagree; there should have been one person/subset of persons responsible for classifying endometritis and another providing systematic treatments. Saline could have been administered in either situation. Thus, subsequent palpators would have been completely unaware of administered treatment.
Results: LeBlanc et al., 2002, cont.

- No difference among groups in uterine involution
- No difference in resolution between 1\textsuperscript{st} and 2\textsuperscript{nd} treatments
- Purulent vs. mucopurulent discharge did not affect pregnancy rates when treatment taken into consideration
- Palpable follicle $>$ CL $>$ no structure for increased pregnancy rate relative to untreated cows.
  - $>$26 DIM, untreated cows had longer median days to pregnancy than treated
    - Spurred stratification between 20–26 DIM and 27–33 DIM
    - Functional CL presence
The author postulated that if prostaglandin is simply lysing the CL, then it should have a similar effect as to when there is not a CL, which was not supported by these results. Though this was not mentioned in the article’s discussion, I postulate that exogenous prostaglandin is more effective at inducing uterine tone and, when rechecked 14 days later, a less severe endometritis was observed. Additionally, there was a negative effect towards pregnancy if a CL was not present which was unexpected. Interestingly, the author cited work by Gay and Upham (1994) which described administration of prostaglandin to a normal CL in early DIM may actually suppress follicular development leading to impaired fertility.
Pregnancy rate curve deviation was most likely attributed to returning to positive energy balance, resulting in increased body condition scoring, and positive influences over the estrus cycle and fertility.
Any provided treatment should generate revenue for the veterinarian. This is a two fold dilemma. The farmer is willing to pay for the infusion due to risk aversion. The veterinarian is willing to provide the service to maintain clientele. Under the perceived notion that infusion will at least provide no harm but a presumed benefit, the practice continues, despite the loss of producer revenue.

This figure was based on a 205 d lactation and the herd risk for pregnancy of 1.18 leading to 37 days longer with a daily cost of $4.70 for every day beyond 85 in milk (Plazier et al., 1997).
Another reason not to infuse...

- A study* investigating ceftiofur infusion or benign neglect 44 DIM after diagnosis of clinical endometritis in concert with prostaglandin administration on days 37 ± 3 and 51 ± 3 d revealed:
  - Interval to pregnancy was the same for both treatments
  - Did not effect pregnancy rates for those animals already receiving progesterone (every animal)
  - Ceftiofur did not decrease subclinical endometritis, but did clinical (51.4%)

A review* of two IU treatments for clinical endometritis out of the UK demonstrated that oxytetracycline (63% resolution) worked better than the antiseptic policresulen (46% resolution) for 107 cows from 7 farms
- No control, no placebo, and cows enrolled as early as 18 days
  - Before accepted definition of endometritis

These types of articles exist
- Just because it was published does not make it scientifically-correct!

Take Home Points

- Infusion is not superior to prostaglandin injection which is not superior to natural clearance
  - Most animals will spontaneously resolve clinical endometritis before 27 d
    - No treatment recommended

- Prostaglandin should be administered first as labeled drug without milk or meat withdrawal
  - Induces estrus; tones uterus
  - Debate over whether multiple injections should be given before further work-up or not

- If clinical endometritis is still present, a vaginoscopy ± culture and sensitivity is warranted
  - Limited in private practice