Current Therapies in Bovine Fertility

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Goals

I. The following should be the goals of dairymen and veterinarians who want to maximize reproductive and milk production efficiencies.
   A. 12-13 month calving interval.
   B. Average days open 85-115 days.
   C. Voluntary waiting period of 45-50 days.
   D. Breeding period of 40-70 days.
   Thus, cows must be detected in heat, inseminated, and become pregnant within three estrous cycles after breeding begins.

II. Two constraints that limit our goals:
   A. Accurate heat detection.
   B. Restoration of the postpartum uterus to a fertile condition.

Normal Postpartum Uterine Involution in Dairy Cows

I. Uterine involution has been described as being comprised of three overlapping processes.[1]
   A. Reduction in size
      a. Rectal palpation has been the method to estimate the time interval from parturition to complete uterine involution.
      b. Period for complete involution ranges from 18-50 days (≈30 days).
      c. Early reduction in size of postpartum uterus results from:
         1. vasoconstriction[2]
         2. peristaltic contraction[3]
   B. *Tissue Loss*
      a. Expulsion of fetal membranes usually occurs within 12 hrs postpartum.
      b. Gradual loss of caruncular endometrium.[1]
         1. Day 5: necrosis, vasoconstriction, and infiltration of leucocytes. May be associated with postpartum uterine production of prostaglandins.
         2. Day 12 to 15: Sloughing of caruncular septum.
         3. Day 19: Caruncles appeared as rough knobs (15-20 mm in diameter) each with a regressing mass of blood vessels.
      c. Two pathways by which waste products of uterine involution are eliminated.[4]
         1. Resorption—regressing cells of the serosa, subserosa, and myometrium.
         2. Desquamation into the uterine lumen—regressed cells of the endometrium.
   C. *Tissue repair*
      a. Tissue loss and repair occur simultaneously up to day 15 postpartum.[5]
      b. Regenerated cells originate from the basal area of the endometrial epithelium.
      c. Regeneration of epithelium over the regressed caruncles occurs from the margin of the caruncles.
         1. Caruncle surface not covered by new epithelium before day 25.
      d. Myometrial changes:
         1. Decrease in myometrial mass by a reduction in cell number and size.[6,7]
         2. Process begins by day 3 postpartum and is complete by day 31.
         3. There is no necrosis of muscle fibers during the regression of the myometrium.
   D. *Factors which affect uterine involution:*
      a. Hasten
         1. Warm seasons
         2. Suckling
         3. High levels of energy and protein (minimal)
         4. Primiparous
      b. Delay
         1. Dystocia
         2. RP/uterine infection
         3. Milk fever
         4. Ketosis

Therapeutic Considerations to Optimize Reproductive Efficiency in the Bovine Animal

I. Postpartum uterine infection:[8] (RP, metritis, pyometra)
   A. **Pathogenic etiologies**
      a. *C. pyogenes*
         1. Primary uterine pathogen.
         2. Aerobic organism.
      b. Gram negative anaerobes.
         1. *Fusobacterium necrophorum*—produces leukocidal exotoxin which diminishes host

Paper presented at the Annual Bovine Seminar, Frederick, Maryland, Sept. 26-27, 1985.

defenses against bacteria.

2. *Bacteroides melaninogenicus* and *Bacillus fragillus* produce and release a substance which prevents bacterial phagocytosis and inhibits bacteriocidal defense mechanisms.
3. There is a pathological synergism between *C. pyogenes* and the gram negative anaeorbes.

c. Coliforms and other incidental bacteria are insignificant as causes of infertility.

d. *Clostridium spp.*—contributes to severe puerperal metritis.

B. Antimicrobial Therapy

a. *Considerations:*

1. Effect of the therapeutic agent upon subsequent fertility.
2. Bacterial organism that is involved.
3. Oxygen tension and tissue debris in the bacterial environment.
4. Pharmacokinetics of the antimicrobial agent.
   -Concentrations of the antimicrobial agent that can be attained at the site of the uterus.
   -Length of time effective concentrations of the antibiotic can be maintained following treatment.

b. *Penicillin*

1. Interferes with cell wall synthesis making the bacteria more susceptible to lysis.
2. Intrauterine infusion: Organisms become resistant to penicillin by producing penicillinase which is released into the resistant bacteria's environment providing protection to the resistant bacteria and other susceptible bacteria as well. *Do not use penicillin to treat mixed infections of the uterus when part of the population is resistant which is the case in early postpartum uterine infections.*

   Later in the postpartum period, local treatment with penicillin has a greater likelihood of being effective because the *variety* of bacteria in the uterus decreases.
3. Systemically: For systemic treatment early in the postpartum period, penicillin is a good choice because it is effective against the bacteria likely to invade the endometrium from the uterine lumen.
4. Dosages: *System dosages* of 5-10,000 IU/Kg provide therapeutic concentrations for 6-12 hrs.

   Intrauterine doses later in the postpartum period of 1 million units of procaine penicillin provides therapeutic levels in both the lumen and endometrium for 30 hours.

c. *Oxytetracycline*

1. Broad spectrum antimicrobial that binds to the 30S ribosomes and inhibits protein synthesis.
2. Tetracyclines gain access to the bacterial cell wall by:
   -diffusion through the outer cell membrane
   -active transport through the inner cell membrane which requires a carrier protein.
3. Bacteria become resistant to oxytetracycline by decreasing uptake, a slow and gradual process. *Resistance* is an individual cell phenomenon that does not affect adjacent susceptible cells; *consequently tetracyclines are effective in the treatment of early postpartum uterine infections in the bovine.*[9,10]
4. *Systemic use:* Pharmacokinetic studies show a need for 11 mg/kg of oxytetracyclines b.i.d. intravenously to maintain a serum concentration of 5 μg/ml in the bovine. Five μg/ml is well below the average MIC of oxytetracycline for *C. pyogenes* isolated from the uterus (20.4 μg/ml), *so systemic therapy would be ineffective to treat postpartum uterine infections.*[11] Plasma to uterine concentrations of oxytetracycline are only slightly greater than 1:1.
5. *Intrauterine therapy:* Drug of choice for the postpartum uterus because the activity of oxytetracycline is only slightly reduced by tissue debris, purulent exudate, and lowered oxygen tension.[11]

   Effective levels of oxytetracycline can be achieved within the uterus by infusing 4 gms of oxytetracycline daily, intrauterine.

d. *Aminoglycosides* (gentamicin, kanamycin, streptomycin, amikacin and neomycin).

1. Bacteriocidal activity by inhibiting protein synthesis at the level of the ribosome.
2. Aminoglycosides require a redox reaction to be actively transported across the bacterial cell membrane. Consequently, oxygen is necessary to allow them to be taken into the cell.[12]
3. *The uterine environment is anaerobic, therefore, aminoglycosides are ineffective for intrauterine therapy.*[13]

e. *Nitrofurazone*

1. Average MIC for *C. pyogenes* is near the concentration of commercial available nitrofurazone solutions with no dilution by intrauterine fluids.
2. Bactericidal or bacteristatic depending on concentration.
3. Inhibited by organic matter.
4. Irritating and induces premature estrus when infused into early diestral cows.

5. In a field trial evaluating treatment of cows with pyometra[14], *nitrofuraxone was detrimental to fertility and, therefore, is not indicated for intrauterine therapy.*

f. *Sulfonamides*
1. Competitively inhibit the enzymatic incorporation of PABA into the immediate precursor of folic acid.
2. Antibacterial action severely limited by:
-blood
-pus
-tissue debris and tissue breakdown products
In this environment, there is a reduced bacterial requirement for folic acid.
3. In the postpartum uterus, necrotic tissue debris and dead leucocytes furnish metabolites necessary for bacterial growth and, therefore, *sulfonamides have minimal activity in the postpartum uterus.*[8]

II. Nonantibiotic Drugs used in the Postpartum Period

A. *Oxytocin*
1. Conflicting reports to the effects of oxytocin for prevention of RP and postpartum uterine infection.
2. In one study, an IM dose of 20 IU oxytocin immediately after parturition and repeated 2-4 hours later reduced the incidence of RP.[15]
3. Uterine atony due to inhibition of oxytocin release may be a cause of RP. Oxytocin release may be inhibited by increased synthesis of endorphins due to the stress and pain of parturition. This is the reason we may see more RP associated with dystocias.
4. The uterotonic effect of oxytocin requires a uterus sensitized by estrogens, therefore, oxytocin will have the most influence within 12 hrs. post calving.

B. *Ergonovine*
1. Few controlled studies using ergonovine.
2. Recommended dose for cattle is 2-5 mg.
3. A 5-20 mg injection of ergonovine at 1-14 days postpartum failed to demonstrate any increased uterine activity, immediately or within several hours of administration.[16]
4. No consistent inprovement of reproductive function has been demonstrated and, therefore, routine use cannot be recommended.

C. *Estrogens*
1. Conflicting reports.
2. Estrogens are associated with a uterotonic effect which may help protect the cow from uterine infections and enhance uterine involution.
3. Estrogens, used as the only treatment for mild to moderate postpartum infections, with or without RP, may be as effective as antimicrobials.[16]
4. *Recommendation:* 3-10 mg estradiol benzoate, estradiol valerate, estradiol cypionate IM, repeated twice at an interval of 3 days.

D. *Intrauterine infusions of disinfectants.* (iodine, chlorhexadine)
1. Few controlled studies have been made.
2. One recent study demonstrated that breedings per conception and days from treatment to conception were higher in cows infused with 5% Lugol's solution than in nontreated controls in the early postpartum period. This concentration of iodine may be irritating to the endometrium requiring a longer regeneration period before a conceptus can be supported.[17]
3. Intrauterine use of disinfectants may suppress uterine defense mechanisms (e.g., phagocytosis) in the early postpartum period.[16]
4. Iodine infusion in cycling cows (later postpartum) with chronic endometritis:
a. Infusion during the early part of the estrous cycle (3-4 days after the previous estrus) induces estrus within 4-7 days. Infusion late in the cycle (days 16-19), on the other hand, prolonged cycle length by 4-5 days.
b. Infusion of Lugol's solution was followed by $PGF_{2\alpha}$ release in a pattern similar to that of a spontaneous estrus.[16]
c. Artificially increasing the number of estrus periods within a short period may be a valuable alternative to antimicrobial use to enhance recovery from endometritis.[16]
d. *Recommendation:* Depending on the size of the uterus, 100-200 ml of 1% Lugol's solution infused into the uterus 3-4 days after the previous estrus. Breeding on the induced estrus might improve conception rates in repeat breeders. If this method is used on clear cases of mild to moderate endometritis, the animal should not be bred on the induced estrus, but rather at the next spontaneous estrus at an appropriate time postpartum.

E. *Gonadotropin-Releasing Hormones (GnRH)*
1. Injection of GnRH reduces the interval from calving to first ovulation and increases the number of ovulations during the first 3 postpartum months.
2. Three criteria must be met for GnRH to improve fertility.[18]
a. Must be given days 12-18 postpartum. If given earlier, the pituitary is unresponsive to GnRH and if given later a prolonged luteal phase results without improvement in fertility.
b. The cow must have had an abnormal peripartum period, i.e., RP or endometritis.

c. The cow must be serviced before 60 days post partum to show a benefit.

3. In one study, however, cows treated with GnRH in the early postpartum period had a significant increase in pyometra.
4. Further research is needed to clarify the role of GnRH as a hormonal treatment for the restoration of normal fertility.

F. *Prostaglandin*

1. Pyometra—accumulation of pus in the uterus concurrent with a persistent CL resulting in anestrus.
   a. Treatment of cows with PGF at luteolytic doses has resulted in a clinical recovery rate of greater than 90%.[19 20]
   b. Approximately 65% of responding cows conceived after treatment.[20]
2. *Ovarian cysts*
   a. 3 types: cystic corpus luteum, follicular cysts, and luteal cysts.
   b. A recent study demonstrated that cows diagnosed rectally as having ovarian cysts responded as well clinically to 25 mg PGF as to 100 μg of GnRH.[21]
   c. No satisfactory explanation exists for the response of cystic cows with low progesterone concentrations to PGF.
   d. Exogenous PGF may promote gonadotropin release but this has not been demonstrated.
3. *Retained Placenta/Metritis*
   a. Endogenous PGF levels are elevated for 10-20 days postpartum in the normal cow[22] and the source of this PGF is probably the uterus.[23]
   b. Cows with a more rapid postpartum uterine involution tend to have a longer duration of PGF.[24]
   c. Cows with longer PGF elevations resume normal estrous cycles sooner after calving.[24]
   d. Earlier cycling results in more estrous periods before breeding and this is associated with increased fertility.[28]
   e. PGF, therefore, may promote uterine involution and be a suitable treatment for metritis but the mechanism for the therapeutic effect is unknown.
      -The therapeutic effect of PGF has been attributed to the luteolytic action of the treatment of metritis by some investigators.
      -Fenprostolene (Bovilene®) administered one time to cows with RP resulted in faster placental expulsion and less metritis.[26] These results would seem to be dependent on a uterotonic property of the drug.
   f. There is evidence that PGF is uterotonic in the bovine, but the clinical significance of this effect is debated.
4. *Unobserved Estrus*
   a. Most common use of PGF in postpartum dairy cows is due to unobserved estrus.
   b. Those cows with a mature CL are eligible for treatment with PGF.
   c. Breeding cows at estrus after PGF give best results. Two inseminations at 72 and 96 hours was superior to single inseminations.[27]
   d. Appointment insemination may be more profitable in herds with poor heat detection.
   e. Factors which affect return to estrus after PGF administration.
      -Heifers and non-lactating adult cows return to estrus faster after PGF treatment than do lactating cows.
      -Nutritional status.
      -Stage of the estrous cycle. Cows return to estrus sooner and more uniformly after treatment in early diestrus (days 7 and 8) than when treated in mid-diestrus (days 9-13).[28] However, cows in early diestrus (days 5-7) are less likely to respond to PGF than cattle in late diestrus.
   f. Generally, lactating dairy cows treated at unknown stages of diestrus will return to estrus 2 to 7 days after treatment.
   g. Fertility of the estrus after successful luteolysis with PGF is equivalent to that of a spontaneous estrus.

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