Control of the Estrous Cycle of the Ewe

AnS 429 lecture
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Federal laws/regulations pertaining to the use of veterinary prescription products in food-producing animals

- Food Drug and Cosmetic Act of 1938 (as amended)
  - veterinary prescription products may be used “by or on the order of a licensed veterinarian”
Veterinary prescription drug use

- veterinarians are “licensed” to practice veterinary medicine on a state-by-state basis
- be sure your veterinarian is licensed in your state of residence
Veterinary prescription drug use

- AMDUCA (animal medicinal drug use clarification act of 1994 [as amended])
- defined:
  - extra-label drug use (ELDU)
  - VCPR (veterinarian - client - patient relationship)
Extra-label drug use

- any use that is NOT in accordance with the approved label use, such as use
  - in a different species
  - for a different purpose
  - at a different dose, frequency, or route of administration
  - etc.
Extra label drug use

- permitted under certain circumstances such as (not an exhaustive list):
  - to save the life of an animal
  - to reduce suffering of an animal when an approved product is not available or is clinically ineffective
Extra label drug use

- can **NOT** be used:
  - to enhance performance, or
  - for production purposes
ELDU requires a valid VCPR

1) DVM has assumed responsibility for making medical judgments regarding the health of the animal, the need for medical treatment, and the client has agreed to follow instructions.
2) DVM has sufficient knowledge of the animal to make a general or preliminary diagnosis of the medical condition
3) DVM is readily available for follow-up and is personally acquainted with the keeping and care of the animal by virtue of:

– examination of the animal

– medically appropriate and timely visit to the premises where the animal is kept
**Recommendation**

- always get a written order from your DVM indicating (as a minimum):
  - name of prescribed product
  - prescribed dose
  - frequency and route of administration
  - withdrawal time
  - intended use of product
Approved products for sheep

- very few
- usually takes ~ 3 years and ~ $40 M to get a product approved for use in food-producing animals
  - Food & Drug Administration
  - Center for Veterinary Biologics (Ames)
Approved products in sheep

- National Research Support Project 7 (NSRP-7)
- also known as Minor Use Animal Drug program
  - A national agricultural program to provide data for the safe and effective use of drugs in minor species

- [www.nrsp7.org](http://www.nrsp7.org)
NRSP-7

- ceftiofur (treats bacterial pneumonia)
- decoquinate (coccidiostat)
- progesterone (CIDR)
- tilmicosin (treat respiratory disease)
Minor Use/Minor Species

- Minor Use and Minor Species (MUMS) Animal Health Act of 2004
- [http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/default.htm](http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/default.htm)
I do NOT promote or condone illegal drug use in sheep or any other food-producing animal.
Control of the ewe estrous cycle

- synchronization of estrus
  - during the breeding season

- induction of estrus
  - in the non-breeding season
  - requires use of gonadotropin hormones (e.g., FSH or eCG)
**Synchronization of estrus**

- **prostaglandin F"2α (PGF)**
  - produced by the ewe (endometrium)
  - kills the corpus luteum (CL) on the ovary
  - ewes with a CL come into estrus in ~ 60-72 hours after exposure to exogenous PGF
Synchronization of estrus with PGF

- pre-requisites for use of exogenous PGF
  - ewe must be cycling
    » must have reached puberty
    » must not be in the non-breeding season
    » must be in the diestrus stage of the estrous cycle
  - ewe should not be pregnant
    » can (but does not always) cause abortion
Synchronization of estrus with PGF

- protocol:
  - give 2 injections 9 days apart

- may induce changes in cervical mucus that interfere with sperm transport
Synchronization of estrus with PGF

- products available:
  - dinoprost (2-3 cc dose)
    » Lutalyse
    » ProstaMate
    » InSynch
  - cloprostenol (1-1.25 cc dose)
    » Estrumate
    » estroPLAN
Synchronization of estrus with PGF

- always wear gloves when handling this product, as it can:
  - alter menstrual cycle
  - cause miscarriage
  - induce bronchial spasms
  - stimulate GI tract
Synchronization of estrus with progesterone

- Progesterone communicates with the hypothalamus to suppress estrus and ovulation.
- Producers can block estrus and ovulation in ewes until the source of exogenous progesterone is removed.
Synchronization of estrus with progesterone

- can administer exogenous progesterone or a progesterone analogue (progestin, progestagen)
Synchronization of estrus with progesterone

Methods of delivery:
1) orally (in the feed)
   - MGA (melengestrol acetate)
   - 0.25 mg/head/day† for 12 days (in season) or 14 days (out of season; requires FSH or eCG)
   - don’t buy an MGA pre-mix with added Cu!

† 0.125 mg in am and 0.125 mg in pm
Synchronization of estrus with progesterone

2) CIDR [controlled internal drug-releasing device]
   - contains progesterone
   - approved for use in the US in November 2009
**Eazi-Breed CIDR™**

**Sheep Insert**

**Active Ingredient:** Progesterone, 0.3 gram per Eazi-Breed CIDR Sheep Insert

*Use:* Induction of estrus in ewes (sheep) during seasonal anestrus. Seasonal anestrus is when ewes do not have regular estrous cycles outside the natural breeding season. Eazi-Breed CIDR Sheep Inserts have not been tested in estrous cycling ewes. Read booklet label before using drug for complete product information.

**WARNINGS:**

*Human Warning:* Avoid contact with skin by wearing protective gloves when handling the inserts. Keep this and all medications out of the reach of children.

*Environmental Warning:* Used (removed) Eazi-Breed CIDR Sheep Inserts still contain some progesterone. Used Eazi-Breed CIDR Sheep Inserts must be stored in a sealable container until disposed. Sealed bag/container with used Eazi-Breed CIDR Sheep Inserts must be properly disposed in accordance with applicable local, state and Federal regulations.

**Residue Warning:** A pre-slaughter withdrawal period is not required when this product is used according to label directions.

**Other Information:**

Store at controlled room temperature 20° to 25° C (68° to 77° F) with excursions between 15° to 30° C (59° to 86° F). To report suspected adverse reactions or questions call Pfizer Animal Health at 1-800-366-5288.

**Inactive Ingredients:** silicone rubber, nylon.

Made in New Zealand

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**DO NOT USE:**

- In ewes with abnormal, immature or infected genital tracts
- In ewes that have never lambed
- An insert more than once. To prevent the potential transmission of venereal and blood borne diseases, the Eazi-Breed CIDR Sheep Insert should be disposed after a single use.

**WHEN USING THIS PRODUCT:**

- In ewes that respond to treatment the onset of estrus generally occurs within 1 to 3 days after removal of the Eazi-Breed CIDR Sheep Insert.
- Make sure to have a sufficient number of rams to adequately breed all ewes with an induced estrus. Breeds of rams may vary in libido in the non-breeding season. Therefore a ewe to ram ratio up to 10:1 is recommended for multi-ewe situations. For single ewe rams, 1:1 for ram lambs and up to 1:1 for parturient rams are recommended.

**YOU MAY NOTICE:**

Clear, clowy, yellow or bloody mucus on the outside of Eazi-Breed CIDR Sheep Insert when removed from ewes. The mucus may be an offensive odor. This is a result of mild irritation to the vaginal lining by the presence of the Eazi-Breed CIDR Sheep Insert, and generally clears between the time of removal and breeding. Such irritation does not affect fertility.

**DIRECTIONS:**

For induction of estrus in ewes (sheep) during seasonal anestrus:

- Administer one Eazi-Breed CIDR Sheep Insert per ewe for 5 days.
- After insert removal, use standard stock breeding procedures to breed ewes at induced estrus.

**Insertion:**

1. Avoid contact with skin by wearing protective gloves when handling inserts.
2. Only use the specially designed Eazi-Breed CIDR Sheep Insert Applicator for administration.
3. Restrains ewes appropriately prior to administration.

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4. Wash the applicator in a non-irritating antiseptic solution, and then apply a veterinary obstetrical lubricant to the end of the applicator.
5. Push the tail end of the Eazi-Breed CIDR Sheep Insert into the applicator taking care to assure that the tail is extending upward through the slot of the applicator and is pointed away from the handle.
6. Fold the wings of the Eazi-Breed CIDR Sheep Insert to make it longer and continue to advance the insert into the applicator until it is fully seated with the tips of the wings protruding from the end of the applicator (Figure 1).
7. Lubricate the protruding tips of the wings of the Eazi-Breed CIDR Sheep Insert with veterinary obstetrical lubricant.
8. Clean the exterior of the vulva with disposable tissue.
9. Open the lips of the vulva and gently place the loaded applicator through the vulva. The slot in the applicator should face down (see Figure 2).
10. Once the loaded applicator is past the vulva slope the applicator slightly upwards (35° - 45° angle) by bowing the handle, and then forward, without forcing, until the applicator is fully inserted or resistance is felt (see Figure 3).
11. Squeeze the finger grips within the handle of the applicator to deposit the Eazi-Breed CIDR Sheep Insert in the anterior vagina (see Figure 4) and then pull the applicator backwards to remove it from the vagina.
12. With the Eazi-Breed CIDR Sheep Insert correctly placed, with the wings open in the anterior portion of the vagina, the tail of the insert should be visible, pointing downward from the vulva of the ewe.

**Removal:**

1. Remove Eazi-Breed CIDR Sheep Inserts by pulling, gently but firmly, on the protruding nylon tail.
2. Eazi-Breed CIDR Sheep Inserts may reverse direction within the vagina; therefore, if the nylon tail of the insert is not visible on the day of removal, check the vagina to determine if an insert is present.
3. Used (removed) Eazi-Breed CIDR Sheep Inserts must be stored in a sealable container until disposed. Sealed bag/container with used Eazi-Breed CIDR Sheep Inserts must be properly disposed in accordance with applicable local, state and Federal regulations.
Synchronization of estrus with progesterone

3) pessary (sponge)
   - MAP (medoxyacetoprogesterone)
     - 60 mg (Repromap)
   - FGA (fluorogestone acetate)
     - 30 mg (out of season)
     - 40 mg (in season)
     - 45 mg (goats; in and out of season); all marketed as Cronogest
Synchronization of estrus with progesterone

- One approved sponge (20 mg FGA) no longer manufactured
- All pessaries have a 12-day (in season) or 14-day (out of season) treatment
- Out of season requires use of gonadotropin hormone (FSH or eCG)
Induction of estrus

- melatonin
  - produced by the pineal gland during hours of darkness
  - requires ≥ 40-day treatment
    » oral daily drench
    » implant

- Regulin implant not approved in the US
**Induction of estrus**

- **biostimulation**
  - can use for “transitional” ewes

- **“ram effect”**
  - sudden introduction of a ram into a group of isolated ewes will cause ~90% to ovulate within 6 days
    - isolate for ≥ 35 days
    - isolate for ≥ ¼ mile
      - isolate from ram fleeces (pheromones)
Biostimulation

- ewes respond to ram introduction:
  - ovulate, with short cycle (CL dies early)
  - ovulate, with normal cycle length
  - ovulate AND exhibit estrus
    » short cycle
    » normal cycle (this one is fertile!!)