



# Using Estradiol Cypionate (ECP®) vs. GnRH in Controlled AI-Breeding Programs



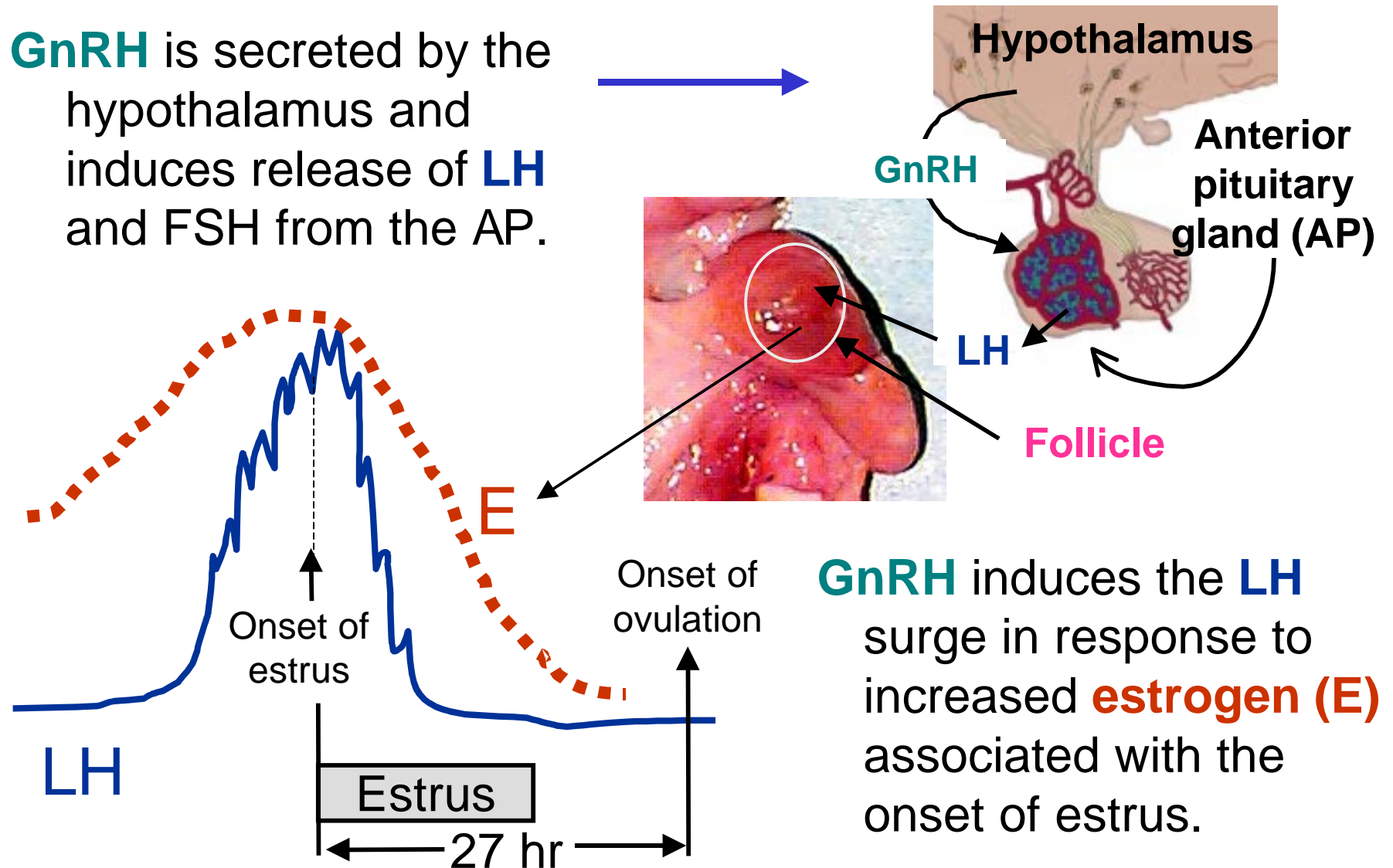
RESEARCH & EXTENSION

# Why Substitute Estrogen for GnRH?



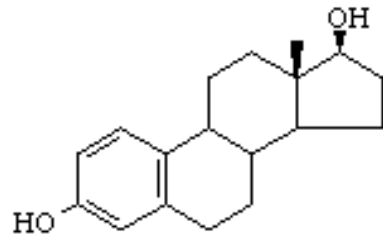
# How Do Estrogen and GnRH Work?

**GnRH** is secreted by the hypothalamus and induces release of **LH** and FSH from the AP.



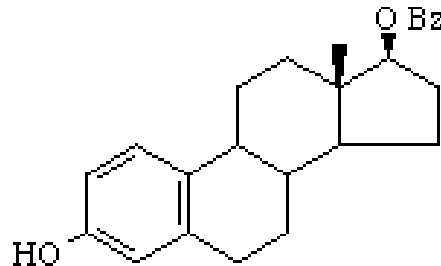
# Estrogens

Estradiol-17 $\beta$



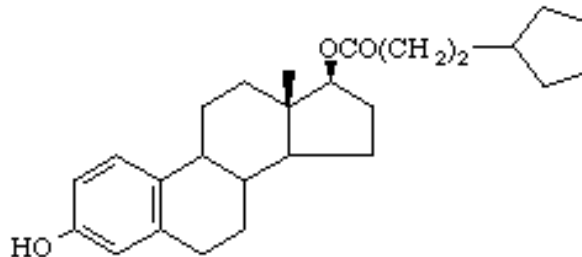
Principal estrogen  
secreted by the follicle

Estradiol  
benzoate



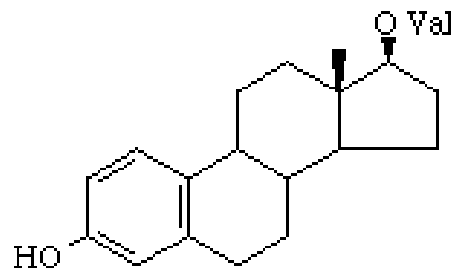
Mimicks estradiol-17 $\beta$  most  
closely (half-life nearly equal)

Estradiol  
cypionate



Longer-acting estrogen  
(sold as ECP®)

Estradiol  
valerate



Longest-acting estrogen;  
was part of Syncro-Mate  
B® estrus-synchronization  
protocol (not available)

# Extra Label Use of Drugs

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- Extra label use means a drug is used for purposes NOT listed as one of its Indications on the bottle label or bottle insert.
- For example, the label for each GnRH product indicates that its approved use is for the treatment of ovarian follicular cysts.
- Use of GnRH in any estrus-synchronization or ovulation control program is considered to be an extra label use.

CYSTORELIN®

Factrel®

FERTAGYL®

OvaCyst®

# Extra Label Use of Drugs

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- GnRH products have therapeutic approvals for use in cattle in the U.S.
- Strict interpretation of Animal Medicinal Drug Use Clarification Act (AMDUCA) is that GnRH products cannot be used for production purposes in cattle.
- However, GnRH products are being used extensively for estrus-synchronization programs by veterinarians and academic researchers who have published their results in scientific journals and producer press.

# Extra Label Use of Drugs

- GnRH is a peptide (very small protein with a short blood half life) with no known health concerns.
- FDA must have minimal concerns regarding use of GnRH products in estrus-synchronization programs because no known prosecutions have been initiated.



# Illegal Use of Drugs and Compounding of Products

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- Estradiol benzoate (EB) has no human or animal approval in the U.S.
- Strict interpretation of AMDUCA is that EB cannot be used for production purposes in cattle.
- Therefore, use of EB in cattle for estrus-synchronization programs is illegal.
- Use of EB also is illegal when compounded with any other approved product.
- Use of the Eazi-Breed™ CIDR® Cattle insert plus Lutalyse® is an **approved** compounding of products.





# What Estrogen is Approved?

- Estradiol cypionate (ECP) has a therapeutic label for use in cattle in the U.S.
- It is the only estrogen approved for use in cattle is ECP® (Pharmacia)
- ECP has multiple label indications including “to correct anestrus [absence of heat period] in the absence of follicular cysts” at 3 to 5 mg doses.



# Use of ECP in Breeding Programs

- Strict interpretation of AMDUCA is that ECP cannot be used for production purposes in cattle.
- Because ECP is an estrogen, it is of concern to the U.S. Food and Drug Administration-Center for Veterinary Medicine relative to human health and safety.

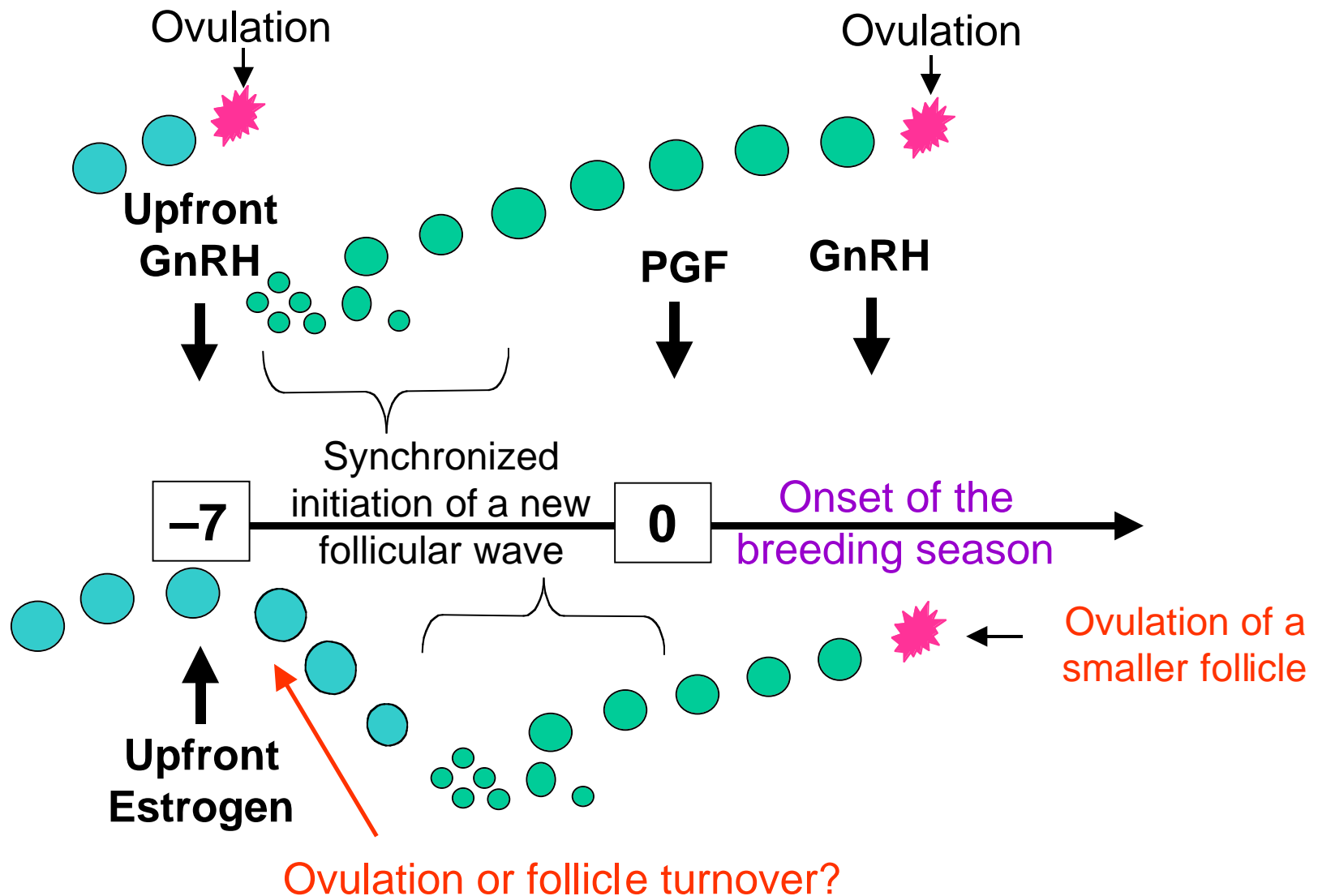


# Use of ECP in Breeding Programs

- ECP is being used extensively for estrus-synchronization programs by veterinarians and academic researchers who have published their results in scientific journals and producer press.
- FDA has not initiated prosecutions of either researchers or veterinarians using ECP in cattle estrus-synchronization programs.



# Follicle Control



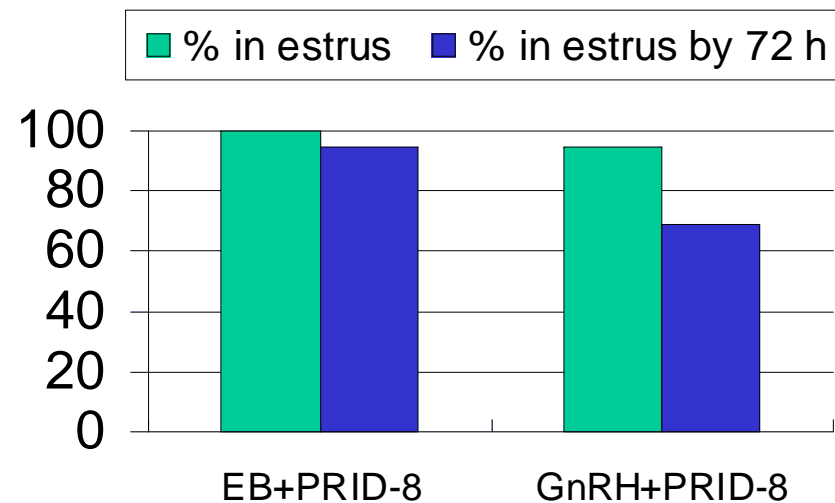
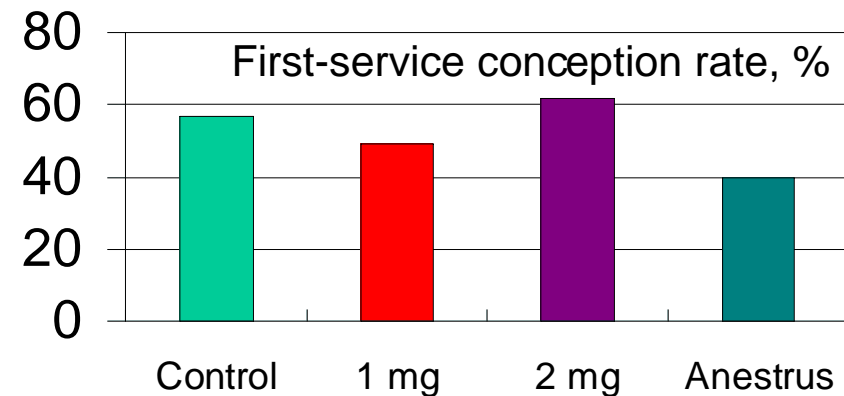
# What Must Estrogen Do To Replace GnRH in Breeding Programs?

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- Estrogen must induce upfront follicle turnover in a synchronization program in cycling cows.
- Estrogen must induce upfront ovulation in anestrus cows.
- Estrogen must induce ovulation after PGF.
- Estrogen must not produce “hyper-estrus” activity to prevent injury of cows caused by excessive riding and standing behavior.
- Estrogen must be easy to administer.

# Upfront Follicular Control?: Cycling

- Upfront EB (1 vs. 2 mg) at CIDR-7 insertion was effective for lactating cycling cows (Day et al., 2000).
- Upfront EB vs. GnRH at PRID-8 insertion was effective in cycling replacement heifers (Lane et al., 2001).



# Upfront Follicular Control?: Anestrus

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- Use of EB at 0.5 or 1.0 mg dose at the time of CIDR insertion did not induce ovulation effectively in seasonally **anestrous** dairy cattle (Verkerk et al., 1998). **Beef cattle?**
- EB + CIDR reduced formation of persistent follicles in lactating **anestrous** dairy cows, but delayed follicular development in some **anestrous** cows (Rhodes et al., 2002). **Beef cattle?**
- Immature dominant follicles in **suckled anestrous** cows were less likely to ovulate after EB (Burke et al., 2001).

# Ovulation after PGF-induced Luteolysis?



Response	Kansas	Florida
<b>ECP</b> to LH surge, h	19.1 ± 2.6	
Onset of estrus after <b>ECP</b> , h	27.8 ± 3.2	29.0 ± 1.8
Duration of estrus, h	6.9 ± 0.7	12.5 ± 1.8
No. of standing events	17.1 ± 5.2	20.3 ± 2.8
Total standing timed, sec	36.3 ± 12	47.6 ± 7.5
Ovulation after estrus onset, h	29.9 ± 2.4	27.5 ± 1.1
Ovulation after <b>ECP</b> , h	60.0 ± 1.8	55.4 ± 2.7

**After luteolysis, ECP induces ovulation in lactating dairy cows and in replacement heifers (Lopes et al., 2000).**

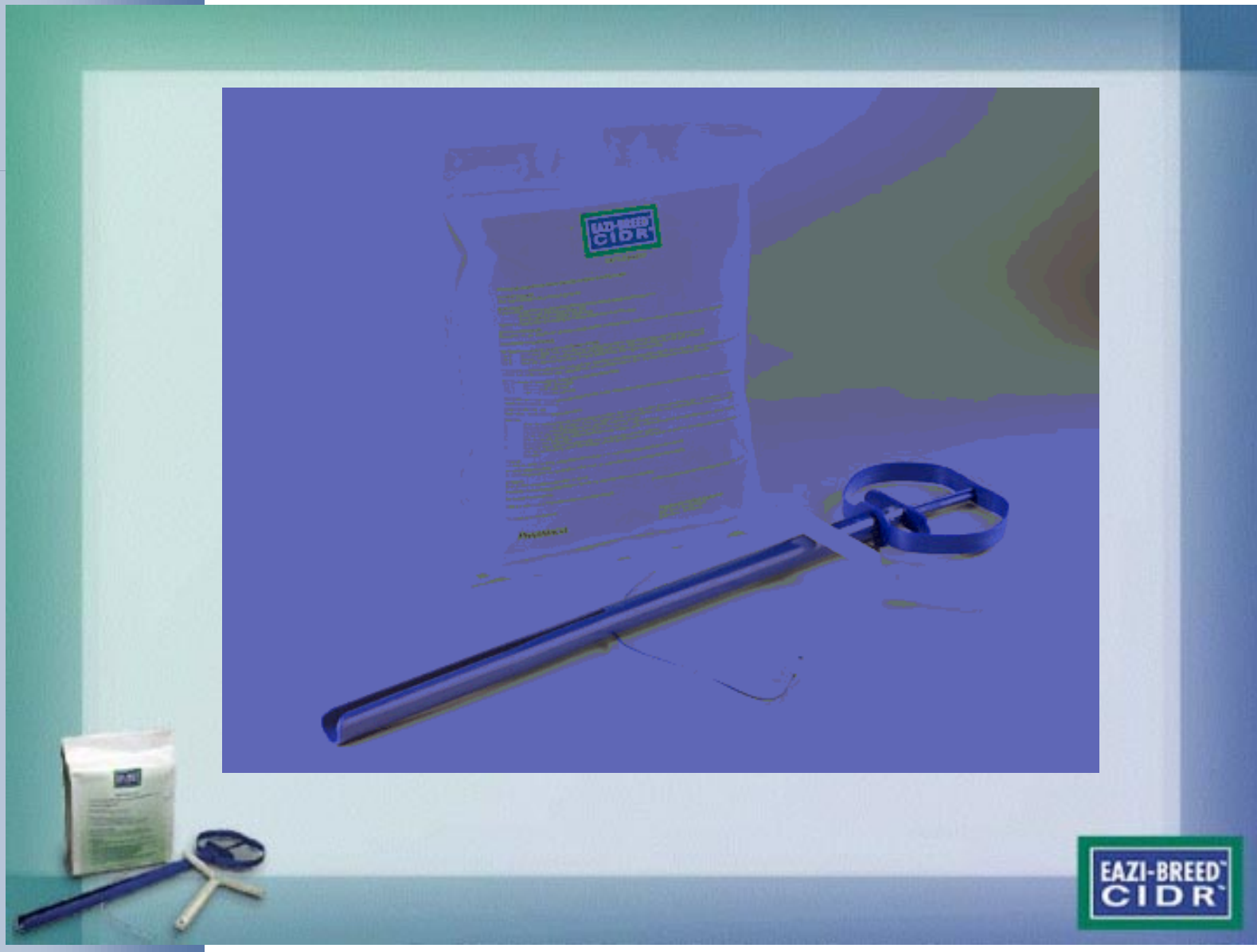


# Easily Administered?

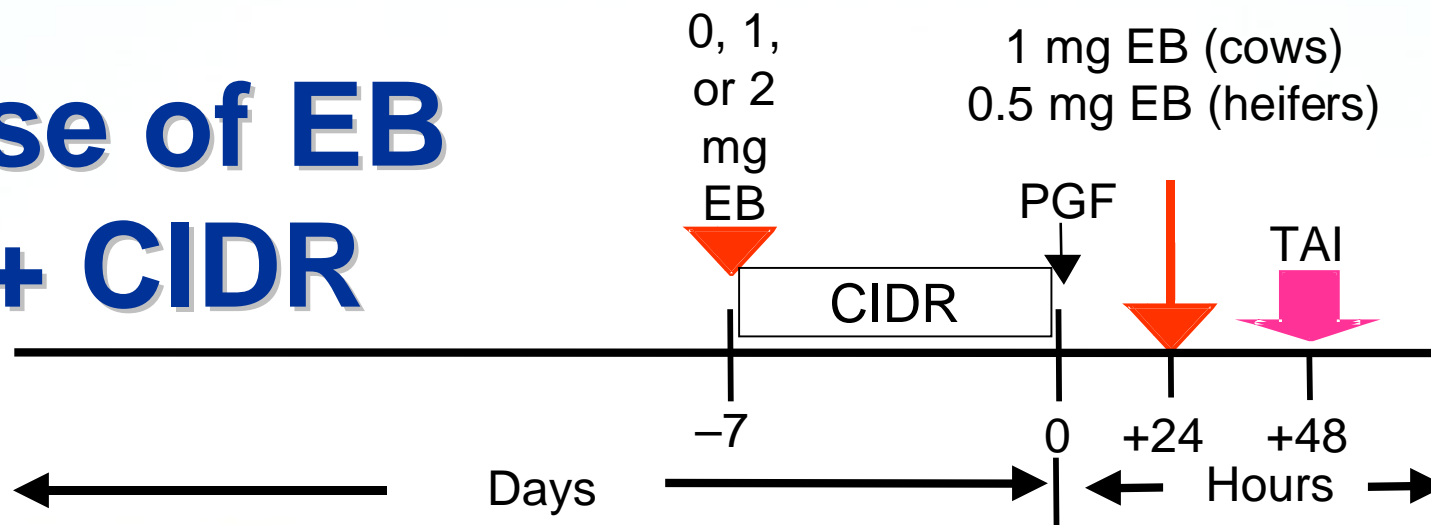
- ECP is dosed at 2 mg per mL.
- A small syringe is required to deliver 1 mg of ECP i.m. in a volume of 0.5 mL (0.5 cc).
- When injecting cows, follow Beef Quality Assurance (BQA) guidelines to reduce carcass bruising and injection site lesions (i.e., use neck injection sites).



# EAZI-BREED CIDR® Cattle Insert



# Use of EB + CIDR

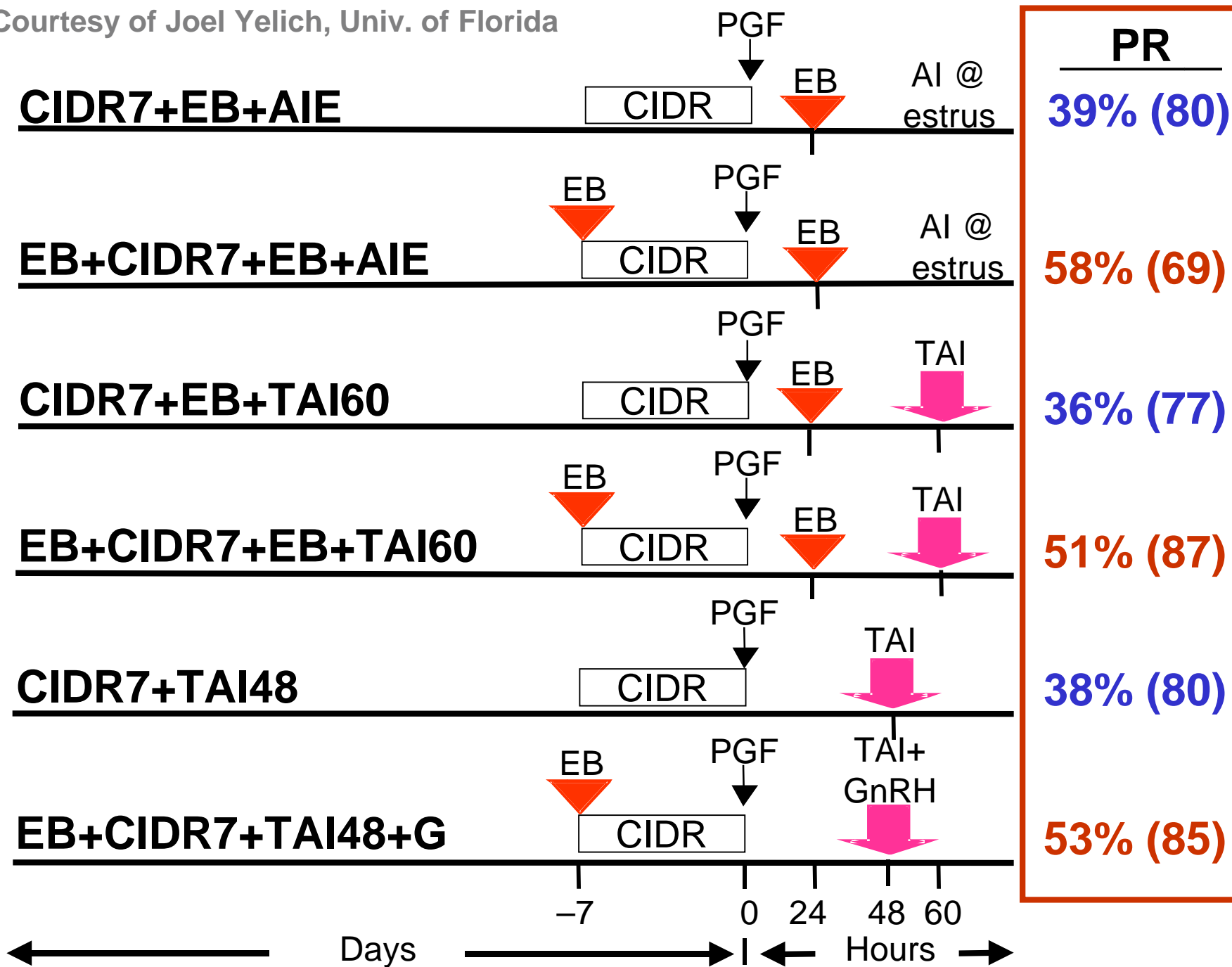


## Pregnancy rates

EB dose	Heifers	Parity 1	Parity 2+
0 mg	43% (56)	28% (37)	64% (73)
1 mg	51% (54)	41% (34)	51% (69)
2 mg	48% (56)	32% (36)	63% (72)

Courtesy of Les Anderson, Univ. of Kentucky

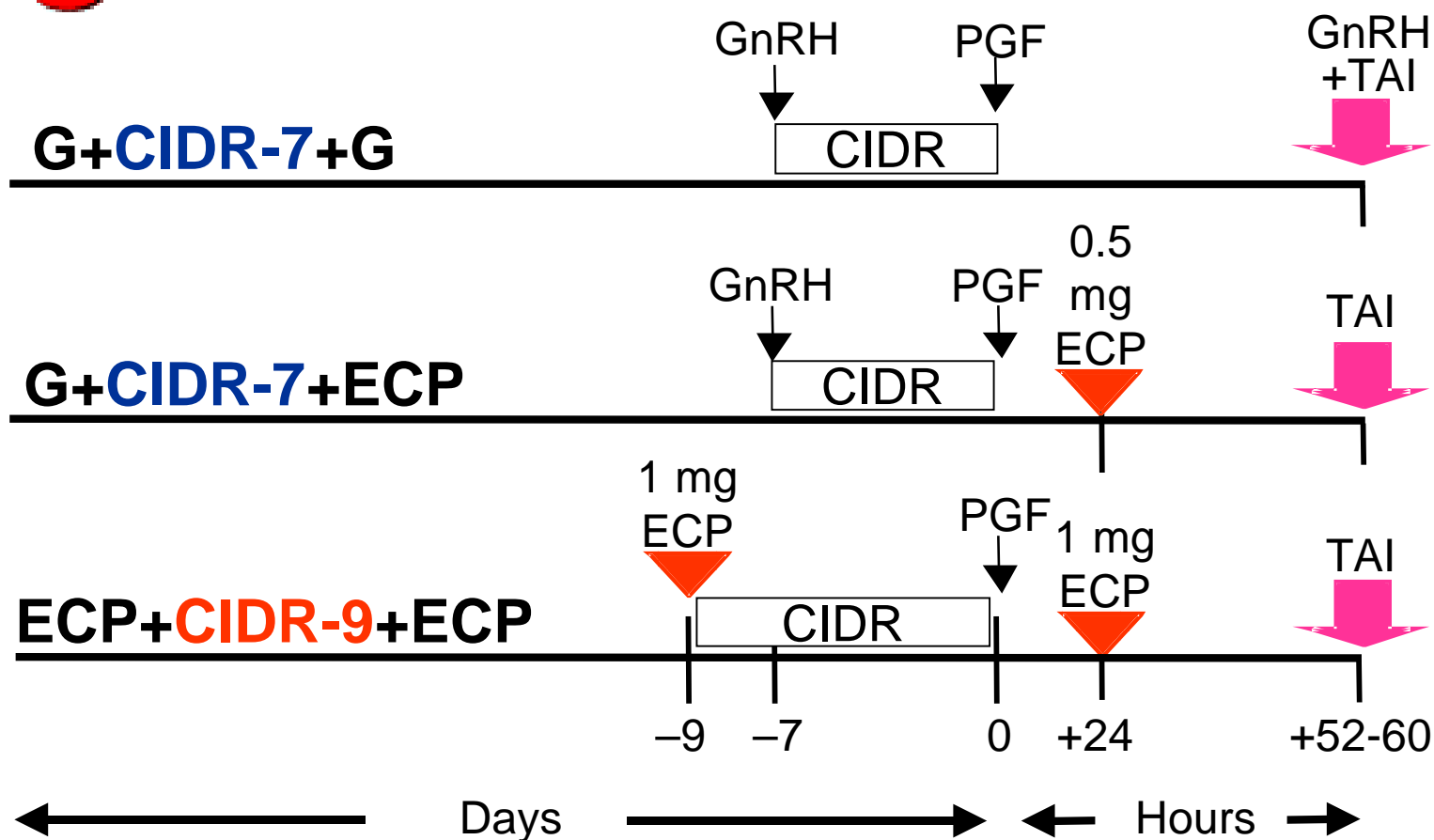
Courtesy of Joel Yelich, Univ. of Florida



courtesy of

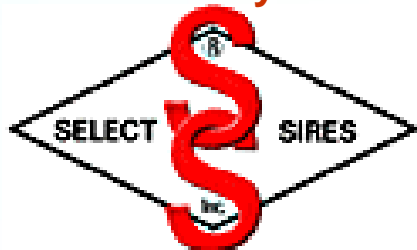


# Use of ECP + CIDR



When using ECP upfront, the CIDR must be in place for 9 days

courtesy of



# Pregnancy Rates in Suckled Angus Cows

Treatment*	Parity 1	Parity 2+	Total
G + CIDR-7 + G	56% (45)	52% (63)	54% (108)
G + CIDR-7 + ECP	61% (44)	72% (60)	67% (104)
ECP + CIDR-9 + ECP	44% (43)	52% (62)	51% (105)

\*TAI at 52 to 60 hr



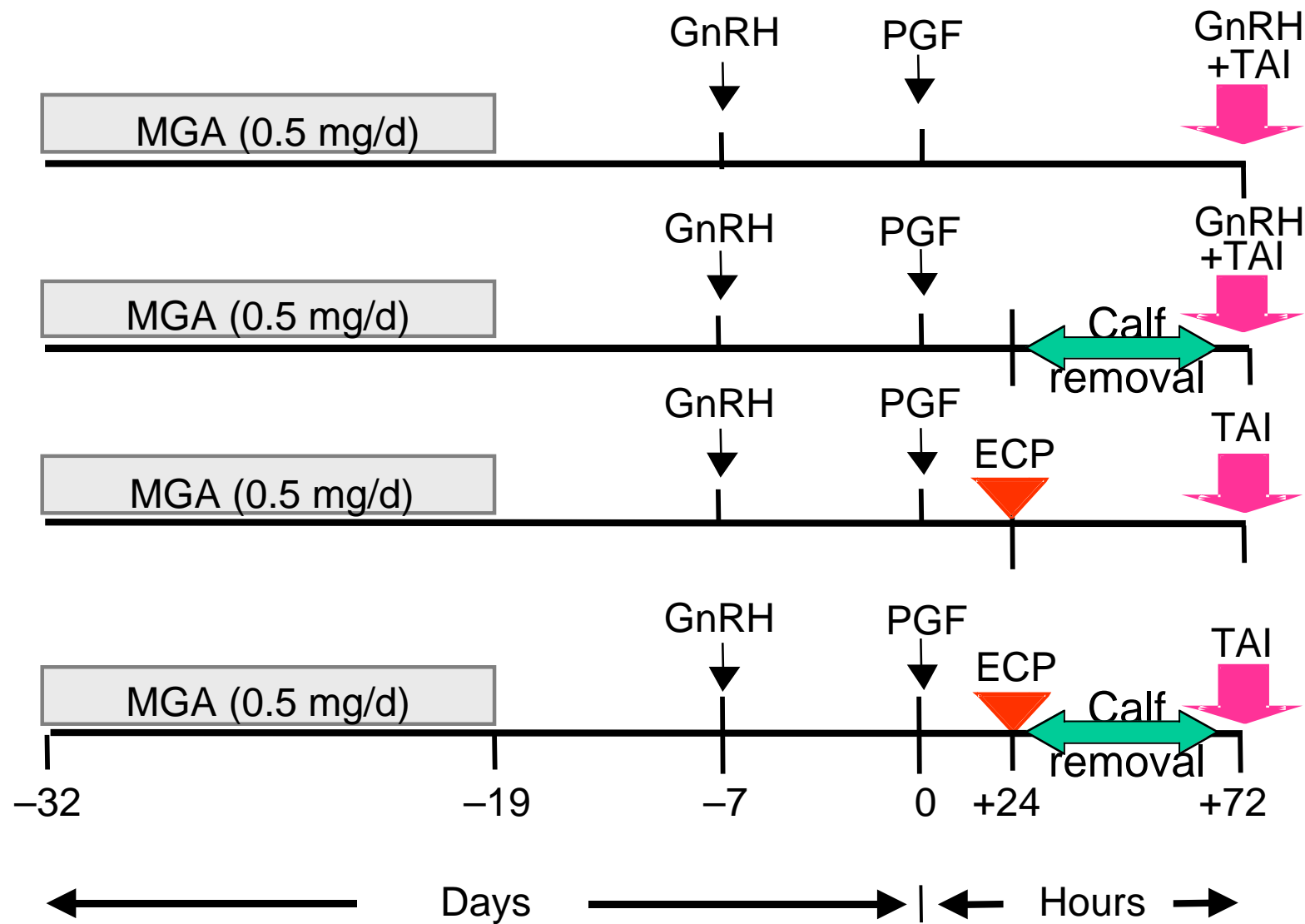
courtesy of



# Pregnancy Rates in Angus Replacement Heifers

Treatment*	Herd B	Herd K	Total
G + CIDR-7 + G	50% (24)	31% (98)	34% (122)
G + CIDR-7 + ECP	33% (25)	39% (99)	38% (124)
ECP + CIDR-9 + ECP	38% (26)	39% (109)	39% (135)

\*TAI at 52 to 60 hr





# ECP vs. GnRH

Calf removal	ECP	GnRH	Total
Yes	49% (94)	51% (97)	50%* (191)
No	51% (90)	38% (88)	44% (178)
Total	50%+ (184)	44% (185)	47% (369)

\*Different ( $P < 0.05$ ) from no calf removal.

+Different ( $P < 0.05$ ) from GnRH.



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# Summary



- ECP is an alternative to GnRH for upfront follicle control, but may not be as effective as GnRH for anestrous cows.
- If ECP is used upfront at CIDR insertion, the CIDR must be in place for 9 days, rather than 7 days when using GnRH.
- After CIDR removal, ECP is an alternative to GnRH after luteolysis for TAI systems.
- Pregnancy rates to TAI tended to be greater in suckled cows when treated after PGF with ECP than GnRH.

# Resynchronization of Estrus

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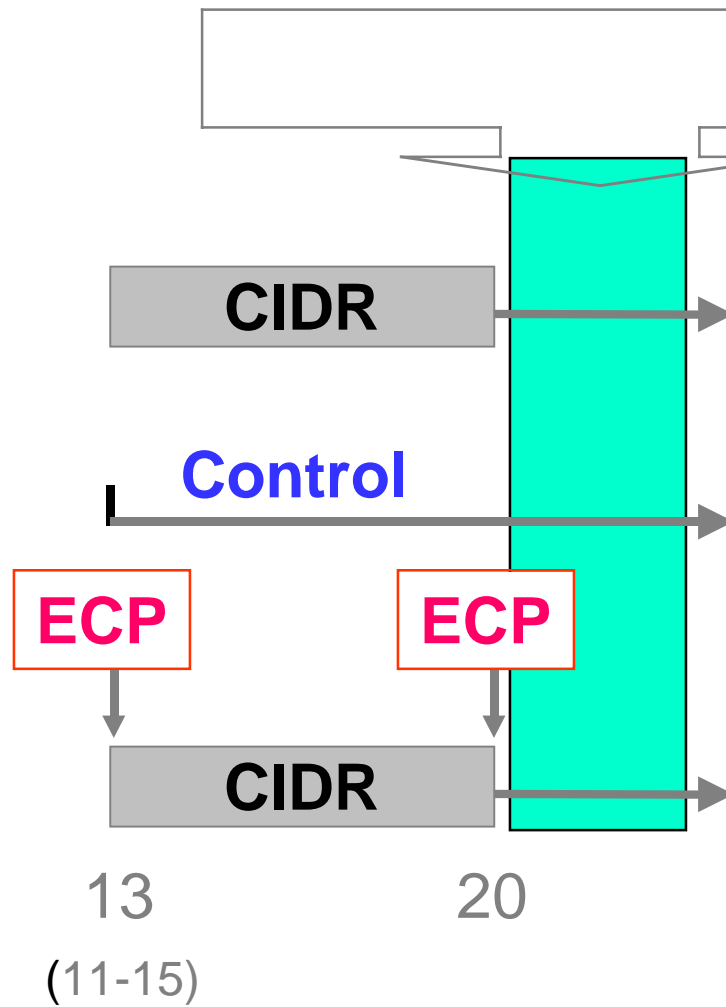
- Increase opportunity for more A.I.-sired calves
- Take full advantage of previous synchrony with little additional cost
- Facilitate heat detection of first eligible heat after A.I.



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# Protocols for Resynchronization of Estrus

- Previously used progestin-releasing inserts or implants
- Feeding of a progestin (e.g., MGA)
- Combination progestins with estrogen injections
- Use of Ovsynch and Heatsynch

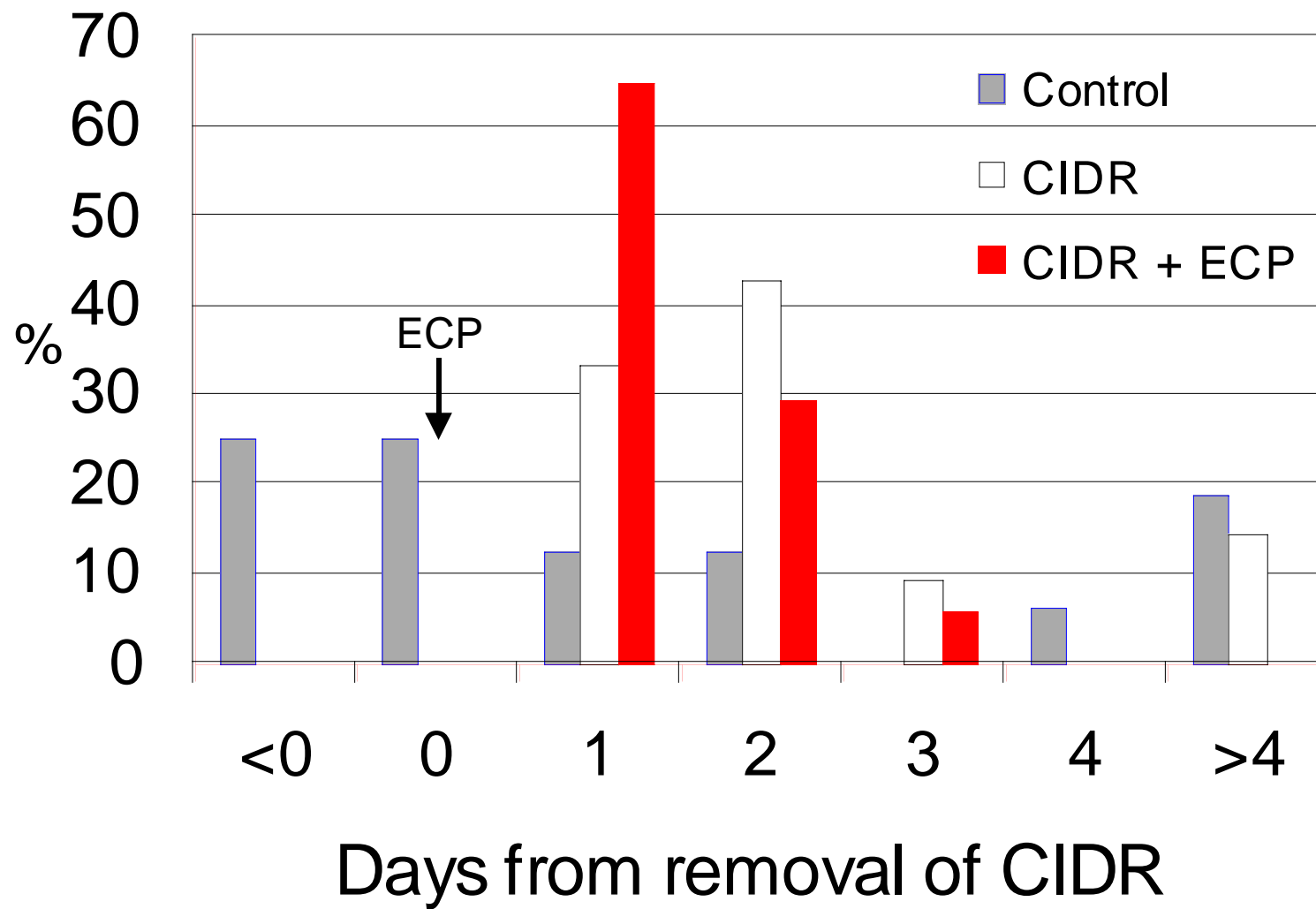


Days after initial AI

Exp. 1:

68 dairy heifers

62 beef heifers

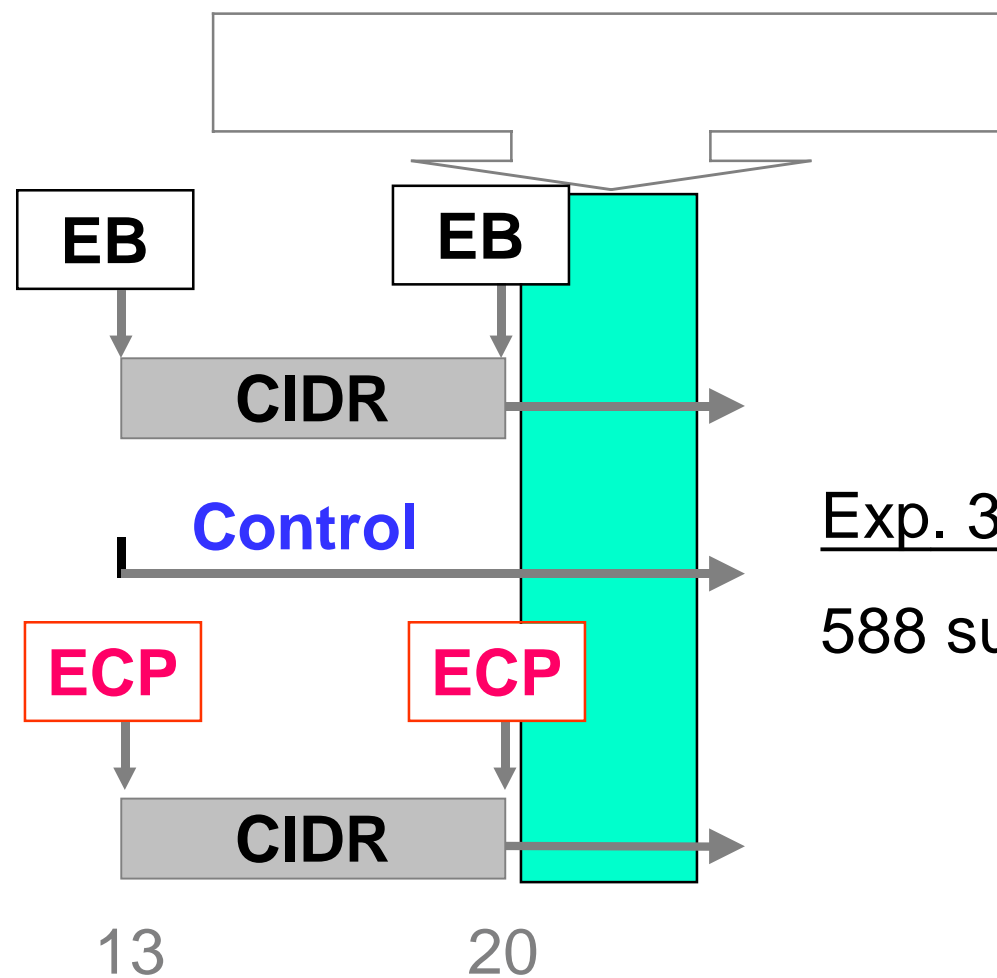


Stevenson et al. 2003. J. Anim. Sci. In press.

# Exp. 1. Reproductive Traits

Item	Con	CIDR	CIDR + ECP
No. of heifers	44	42	44
PR after 1 <sup>st</sup> A.I.	53%	47%	60%
Return 18-26 days	73%	84%	90%
CR of repeat A.I.	60%	33%	35%
26-day PR	72%	60%	73%

Stevenson et al. 2003. J. Anim. Sci. In press.

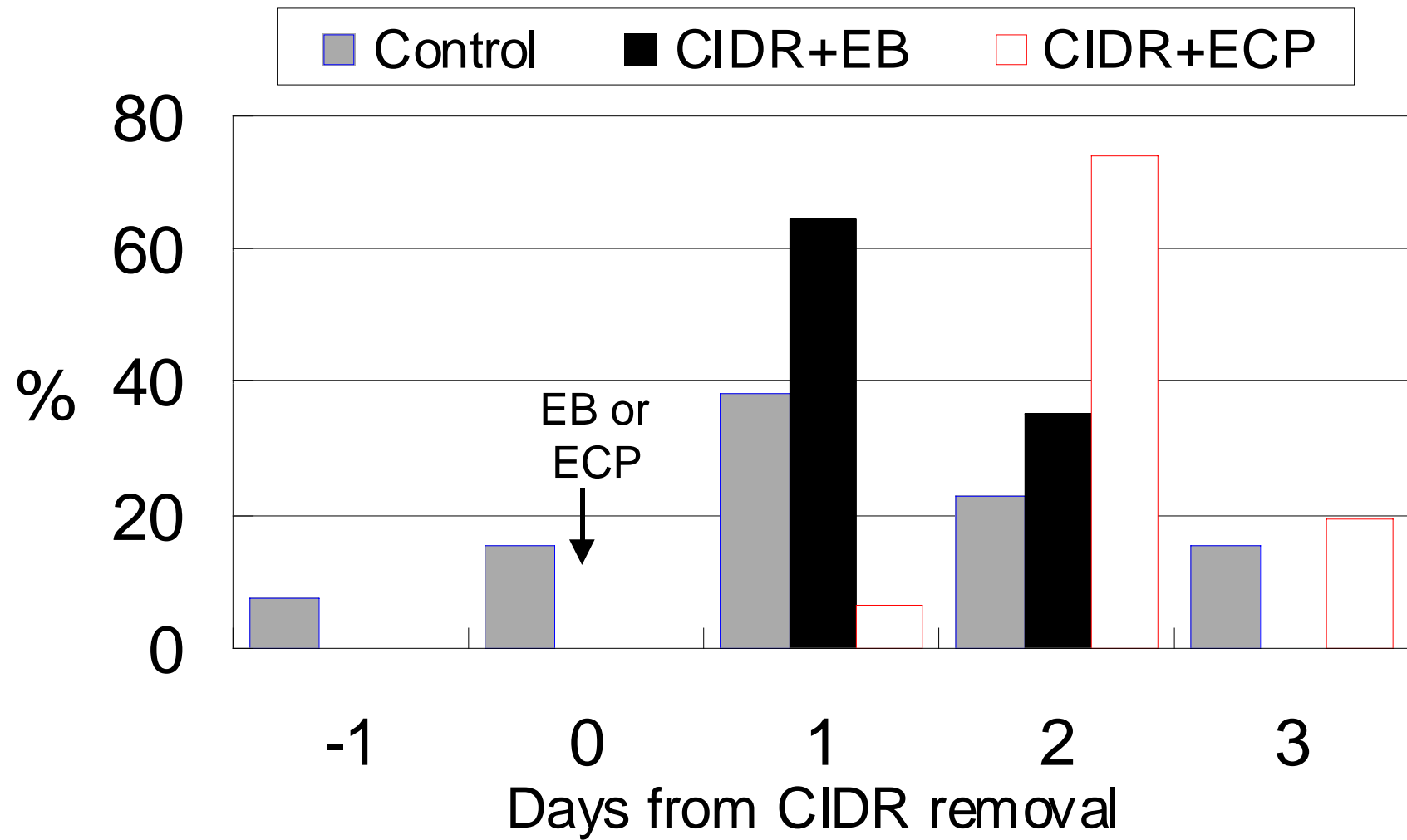


Exp. 3:

588 suckled beef cows

Days after initial TAI





Stevenson et al. 2003. J. Anim. Sci. In press.

## Exp. 2. Reproductive Traits

Item	Con	CIDR + EB	CIDR + ECP
No. of cows	292	151	145
PR after 1 <sup>st</sup> A.I.	52%	44%	52%
Return 20-23 days	29%	84%	65%
CR of repeat A.I.	65%	52%	65%

Stevenson et al. 2003. J. Anim. Sci. In press.

# Summary

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## Resynchronization of repeat estrus:

- Had no negative effect on established pregnancies.
- Increased synchrony of repeat estrus.
- Tended to reduce resynchronized conception rates after resynchronization in dairy and beef heifers .
- Produced normal conception rates at the resynchronized estrus in suckled beef cows when ECP + CIDR were used.

# Thanks to the following for their financial or product support:



- **Select Sires**

- Pharmacia Animal Health
- Fort Dodge Animal Health
- Intervet
- Merial

