Vet school deja vu: practical repro physiology with emphasis on estrus and synchronization of ovulation

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February 4th, 2023

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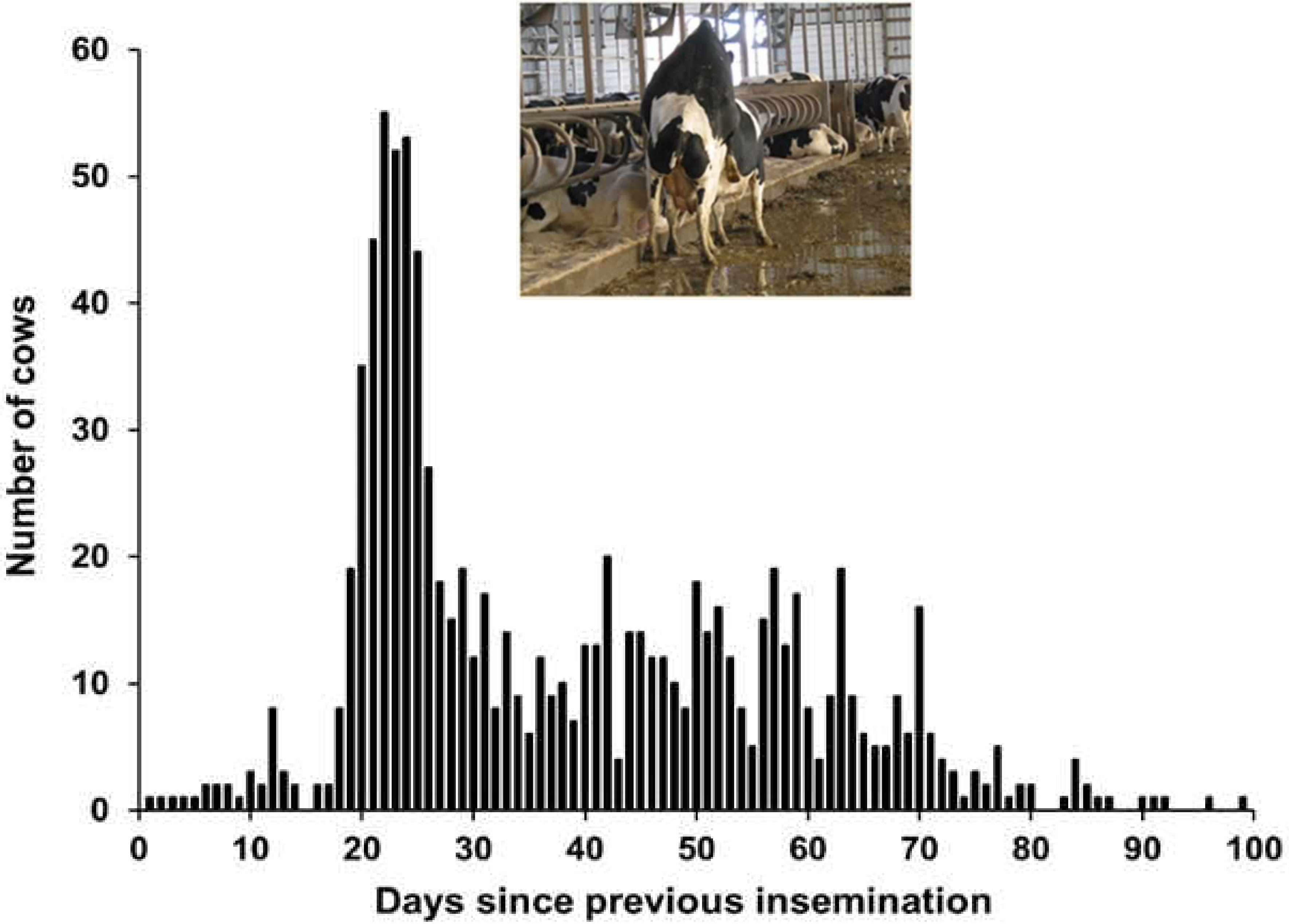
Estrus biology has implications for reproductive management

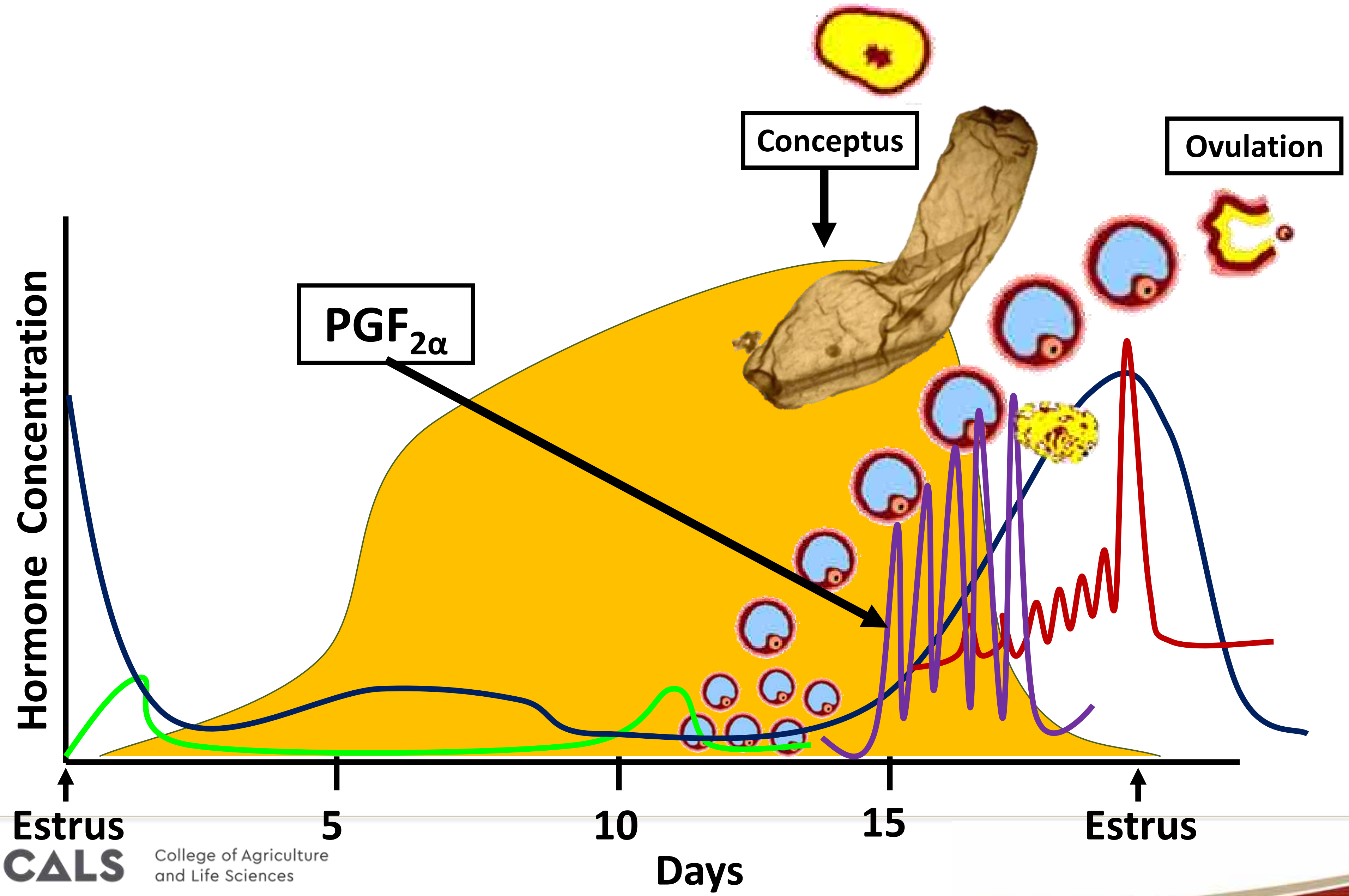
- Effect of early pregnancy loss on expression and detection of estrus

- Expression of estrus during early lactation (VWP) is an indicator of early lactation outcomes and a predictor of reproductive performance
    - Might be used as indicator of good management and predictor for targeted management

Biological events that occur during pregnancy affect return to estrus



Maternal Recognition of Pregnancy



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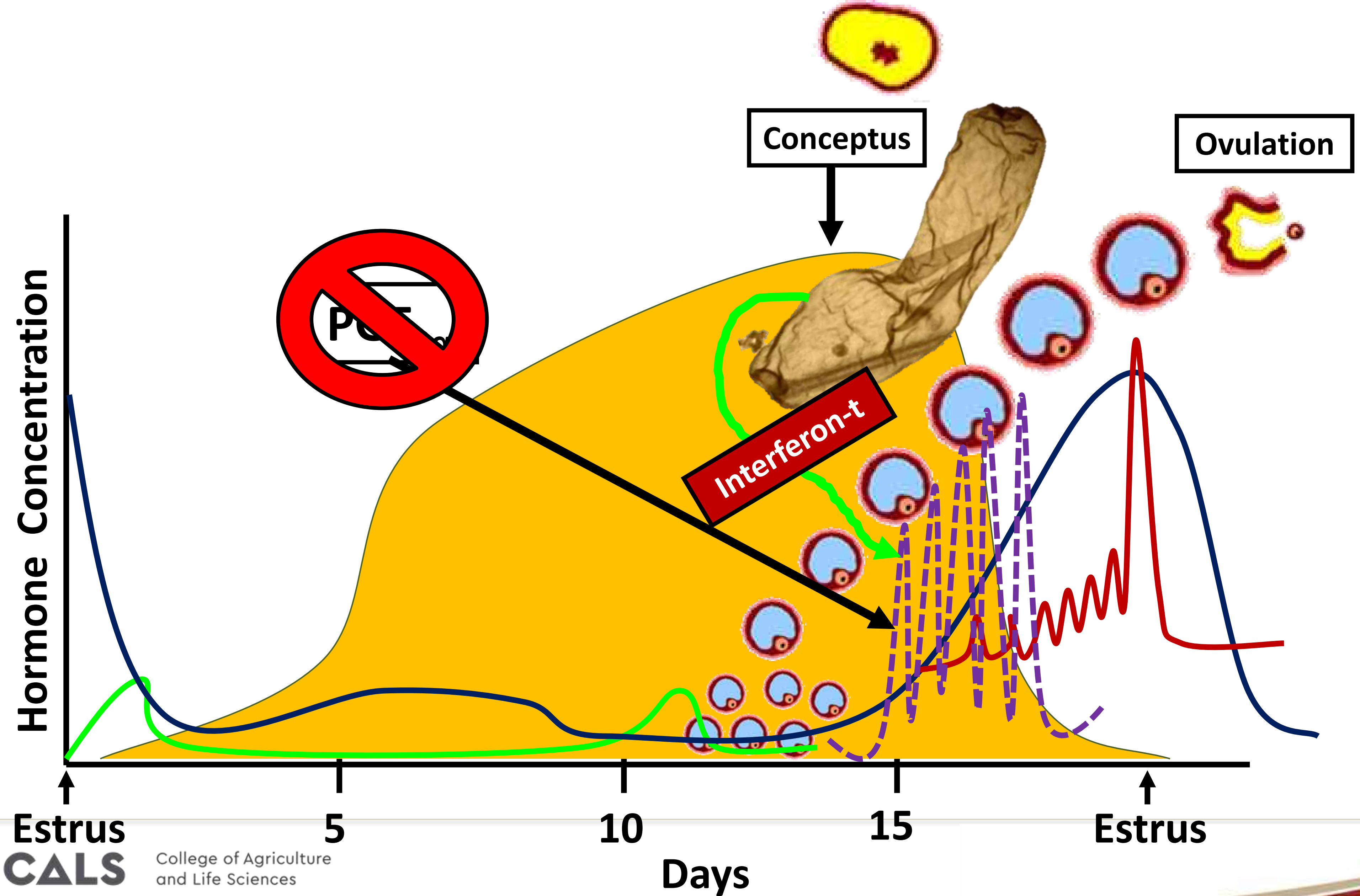
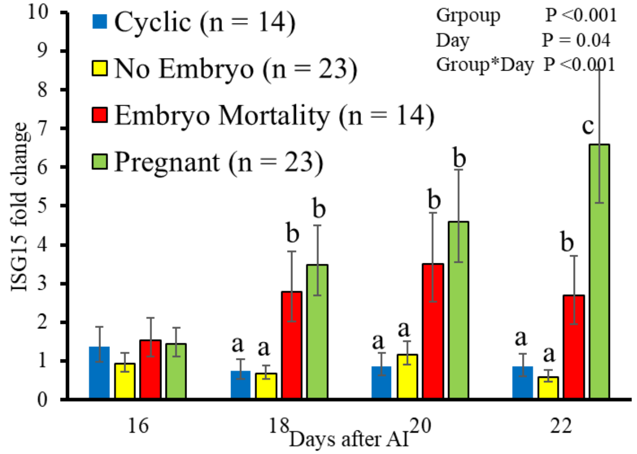


Pregnancy Loss Affects Ovarian Function

BIOLOGY OF REPRODUCTION (2016) 95(5):112, 1–14
Published online before print 5 October 2016.
DOI 10.1095/biolreprod.116.142075

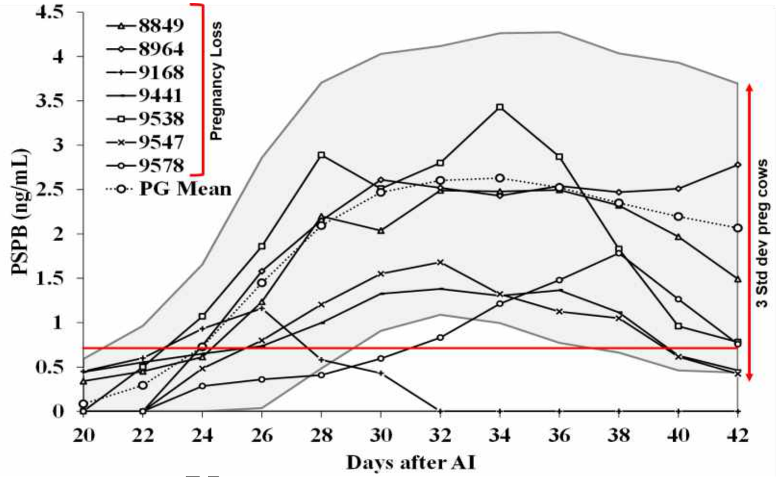
Embryo Mortality Around the Period of Maintenance of the Corpus Luteum Causes Alterations to the Ovarian Function of Lactating Dairy Cows[1]

Robert Wijma,[3] Matias L. Stangaferro,[3] Manasi M. Kamat,[4] Sreelakshmi Vasudevan,[4] Troy L. Ott,[4] and Julio O. Giordano[2,3]



Evidence of Embryo presence based on ISG and PSPB

62% (37/63)

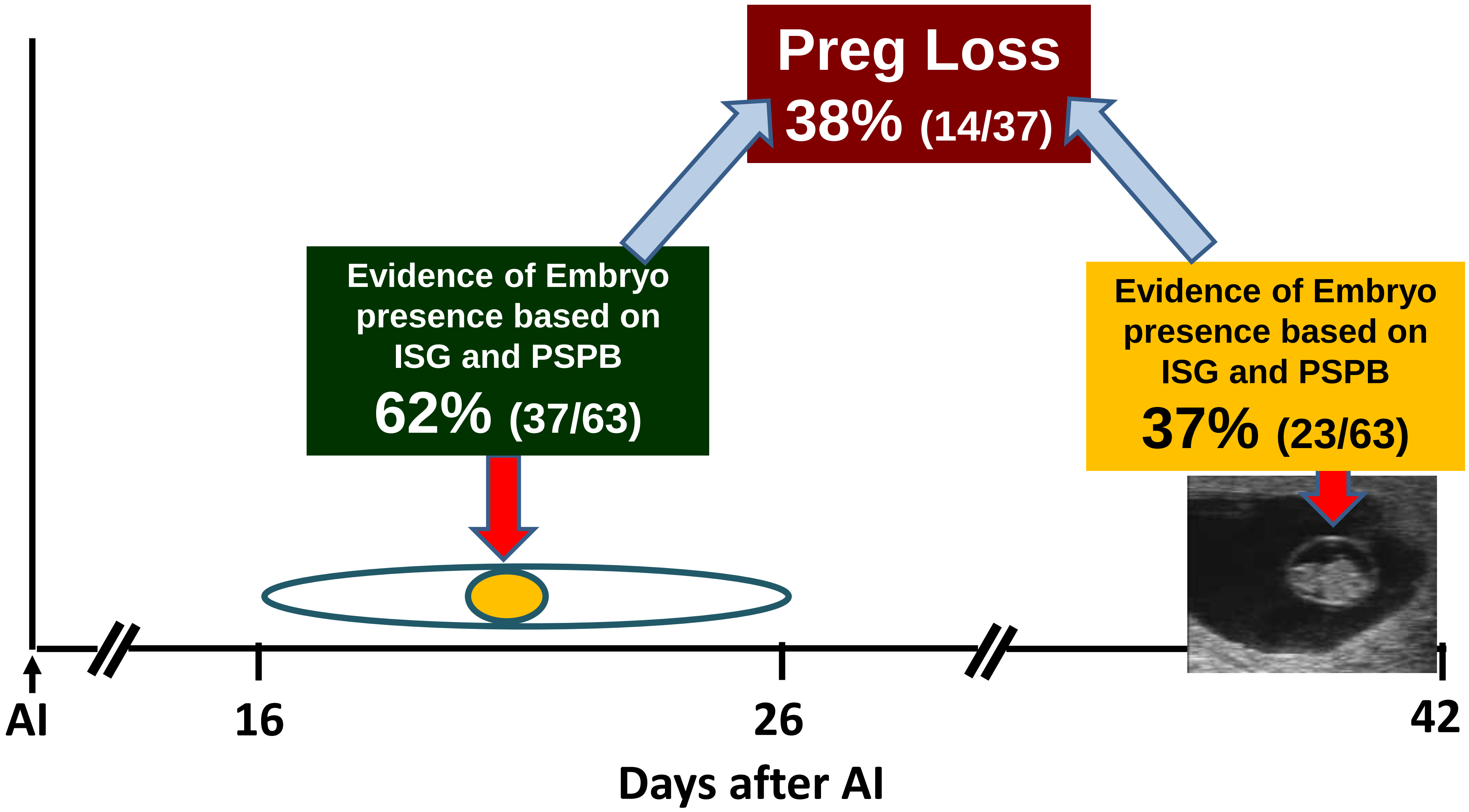


AI 16 26 42

Days after AI

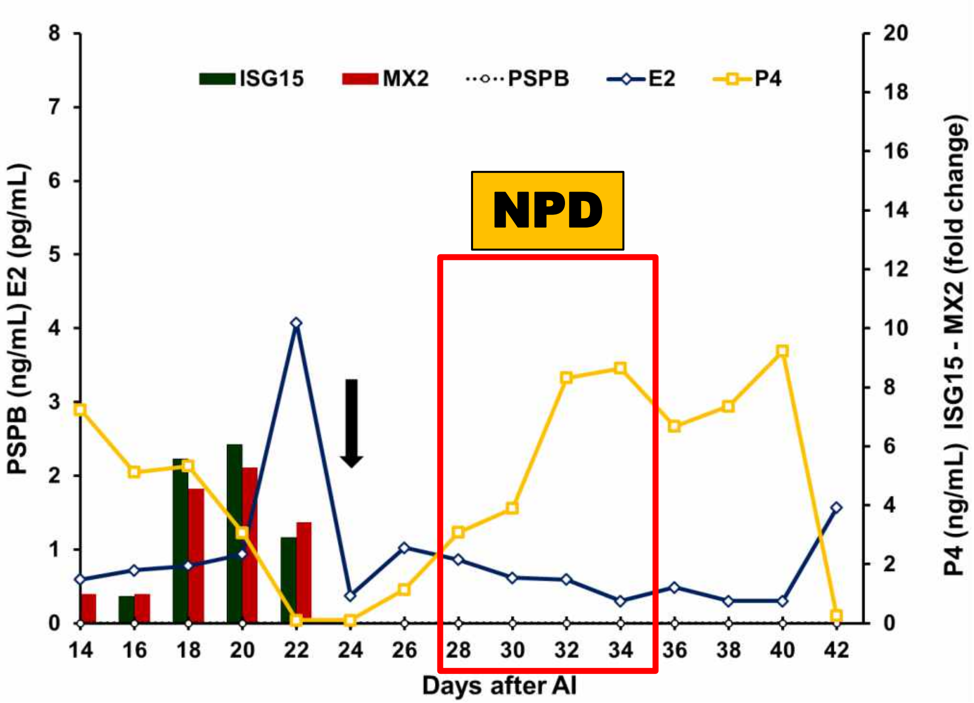
Wijma et al., 2016 (BOR 95(5):112)

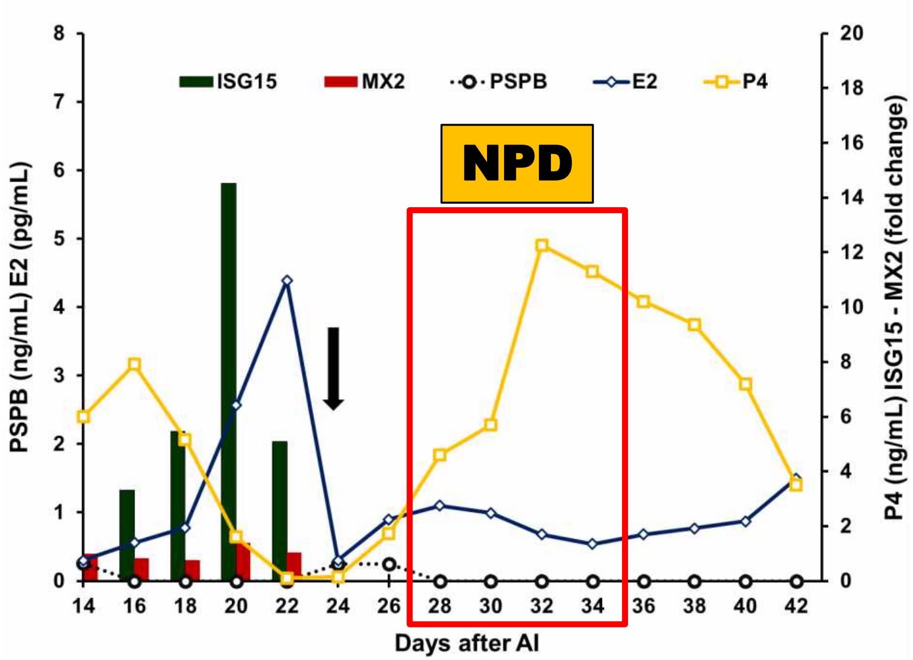
Pregnancy Loss Affects Ovarian Function



Wijma et al., 2016 (BOR 95(5):112)

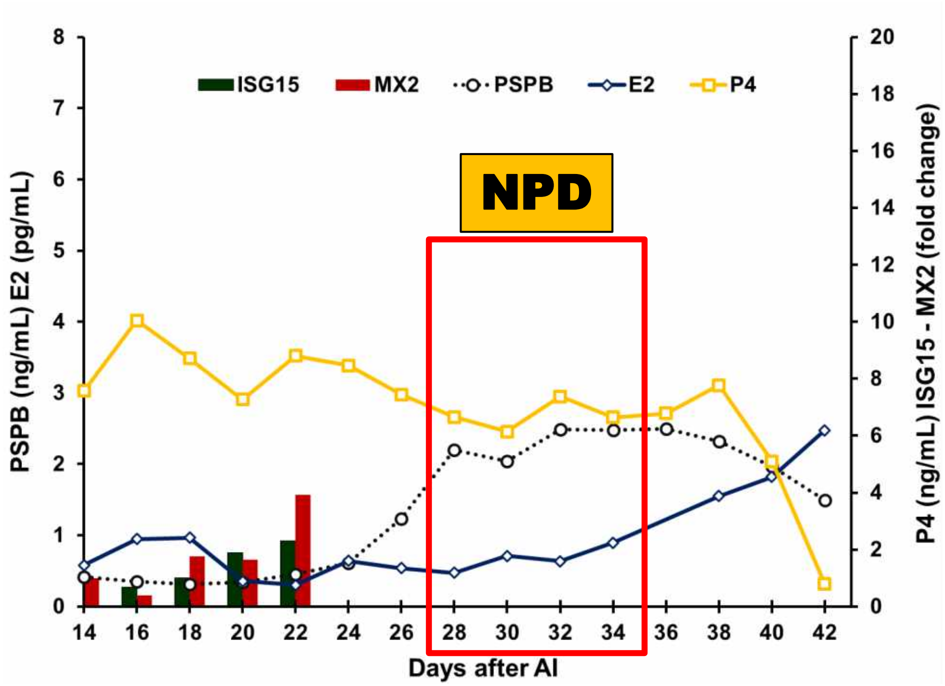
Cows with Early Embryo Mortality (<22 d after AI) return to estrus earlier

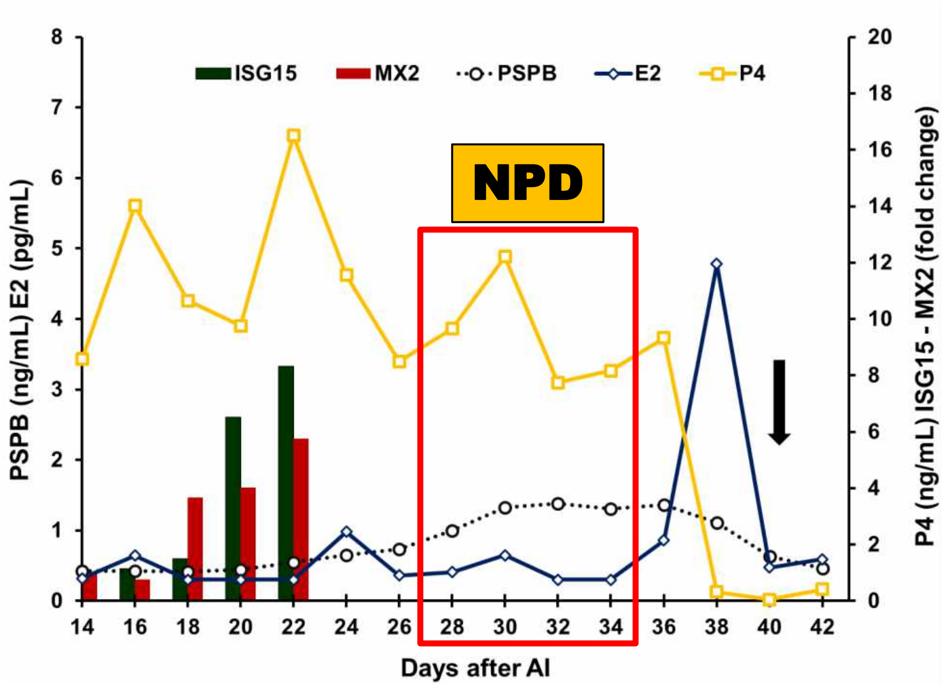




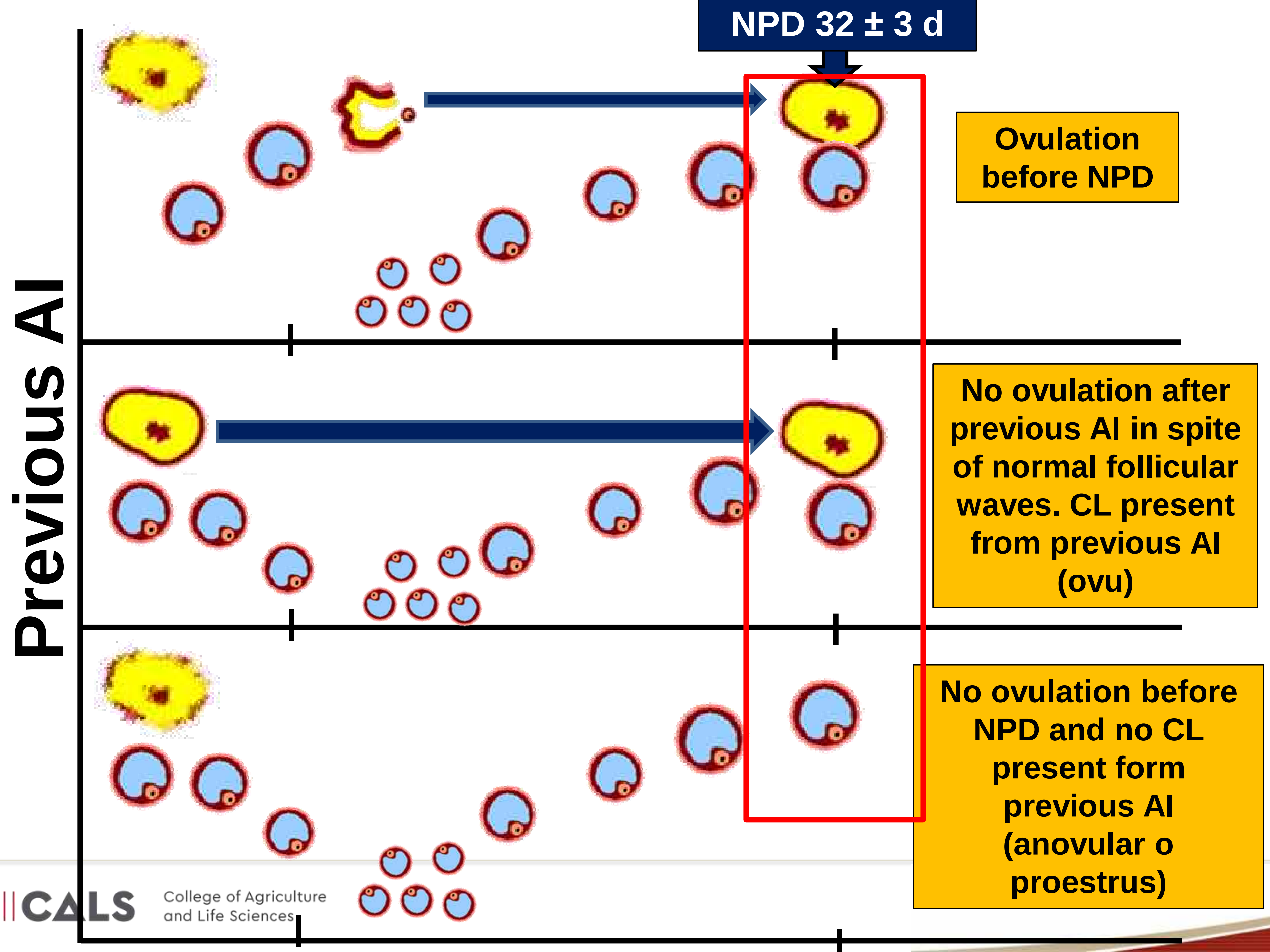
Wijma et al., 2016 (BOR 95(5):112)

Cows with <u>Late</u> Embryo Mortality (>22 d after AI) return to estrus <u>later</u>





Wijma et al., 2016 (BOR 95(5):112)


NPD 32 ± 3 d
Previous AI
Ovulation before NPD
No ovulation after previous AI in spite of normal follicular waves. CL present from previous AI (ovu)
No ovulation before NPD and no CL present form previous AI (anovular o proestrus)

Estrus biology has implications for reproductive management

- Effect of early pregnancy loss on expression and detection of estrus

- Expression of estrus during early lactation (VWP) is an indicator of early lactation outcomes and a predictor of reproductive performance
  - Might be used as indicator of good management and predictor for targeted management

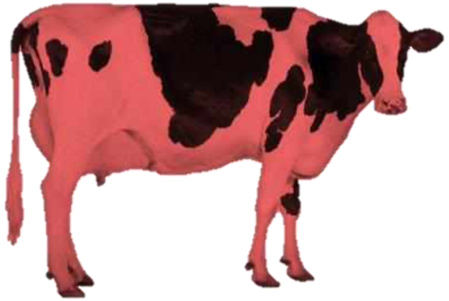
Monitored estrus during the VWP with automated estrus alert (AEA) system

AEA = automated estrus alert

21 DIM

49 DIM

ESTRUS before 50 DIM (VWP)	NO ESTRUS before 50 DIM (VWP)
54.2% (705/1,300)	45.7% (595/1,300)



Rial et al., 2021 J. Dairy Sci. Volume 104, E-Supplement 1

Cows with AEA during VWP more likely to be AIE, conceive at 1st AI, and be preg. at 150 DIM

AEA = automated estrus alert

21 DIM 49

GROUP				
	E-VWP	NOE-VWP	% points diff.	*P*-value
Cows AIE, %	84.9 (416/490)	48.5 (197/406)	36.4	<0.01
All P/AI, %	47.7 (331/693)	42.2 (247/585)	5.5	0.02
Preg 150 DIM	84.9 (390/459)	66.7 (320/417)	18.2	<0.01

Rial et al., 2021 J. Dairy Sci. Volume 104, E-Supplement 1

Monitored cows based on automated estrus alert (AEA) during the VWP

AEA = automated estrus alert

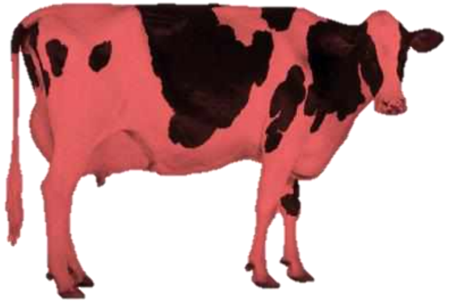
15 DIM — 49 DIM

ESTRUS before 50 DIM (VWP)

59.7% (507/849)

NO ESTRUS before 50 DIM (VWP)

40.3% (342/849)



Cows with AEA during VWP more likely to be AIE and had greater P/AI to 1st service

AEA = automated estrus alert

15 DIM 49

GROUP				
	E-VWP	NOE-VWP	% points diff.	*P*-value
Cows AIE, %	87.9 (218/248)	42.5 (68/160)	45.4	<0.01
All P/AI, %	43.1 (107/248)	23.2 (37/160)	19.9	<0.01
Preg 150 DIM	73.8 (107/145)	57.3 (55/96)	16.5	0.02

Proportion of cows with automated estrus alerts (AEA) during the VWP

AEA = automated estrus alert

21 DIM

49 DIM

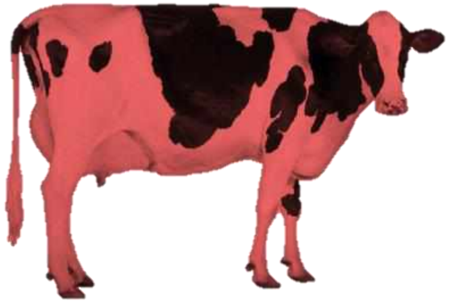
AEA = automated estrus alert

15 DIM

49 DIM

ESTRUS before 50 DIM (VWP)
56.4% (507/2,149)

NO ESTRUS before 50 DIM (VWP)
43.6% (937/2,149)



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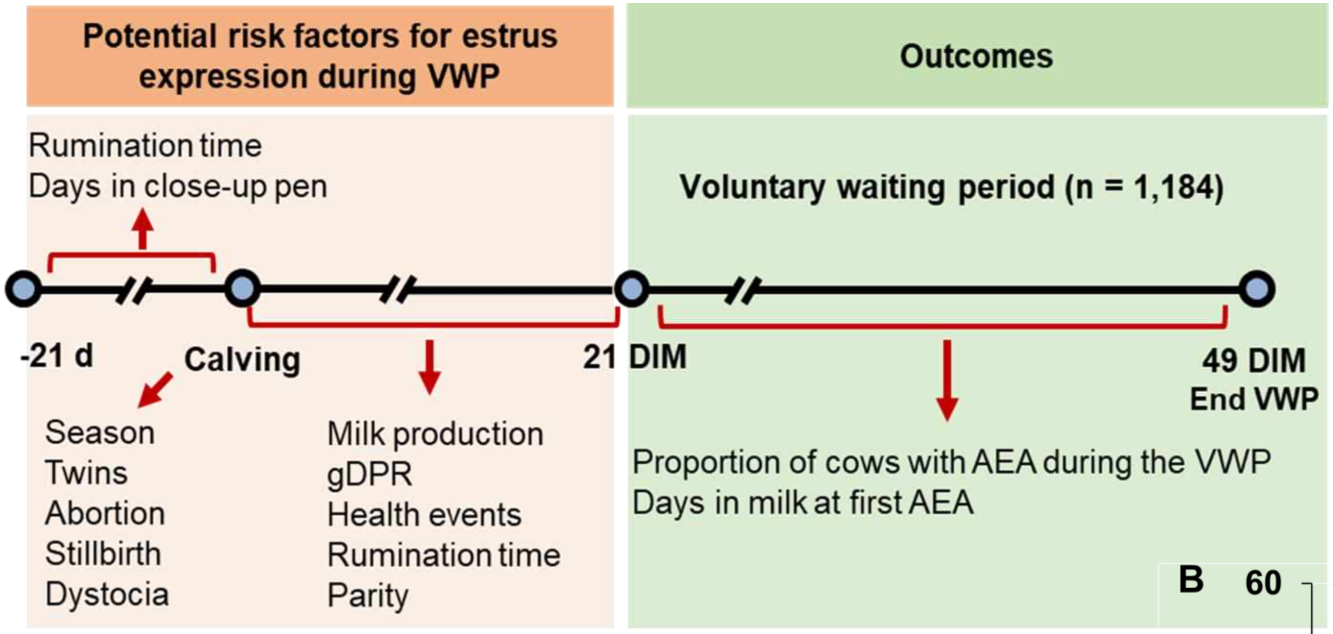
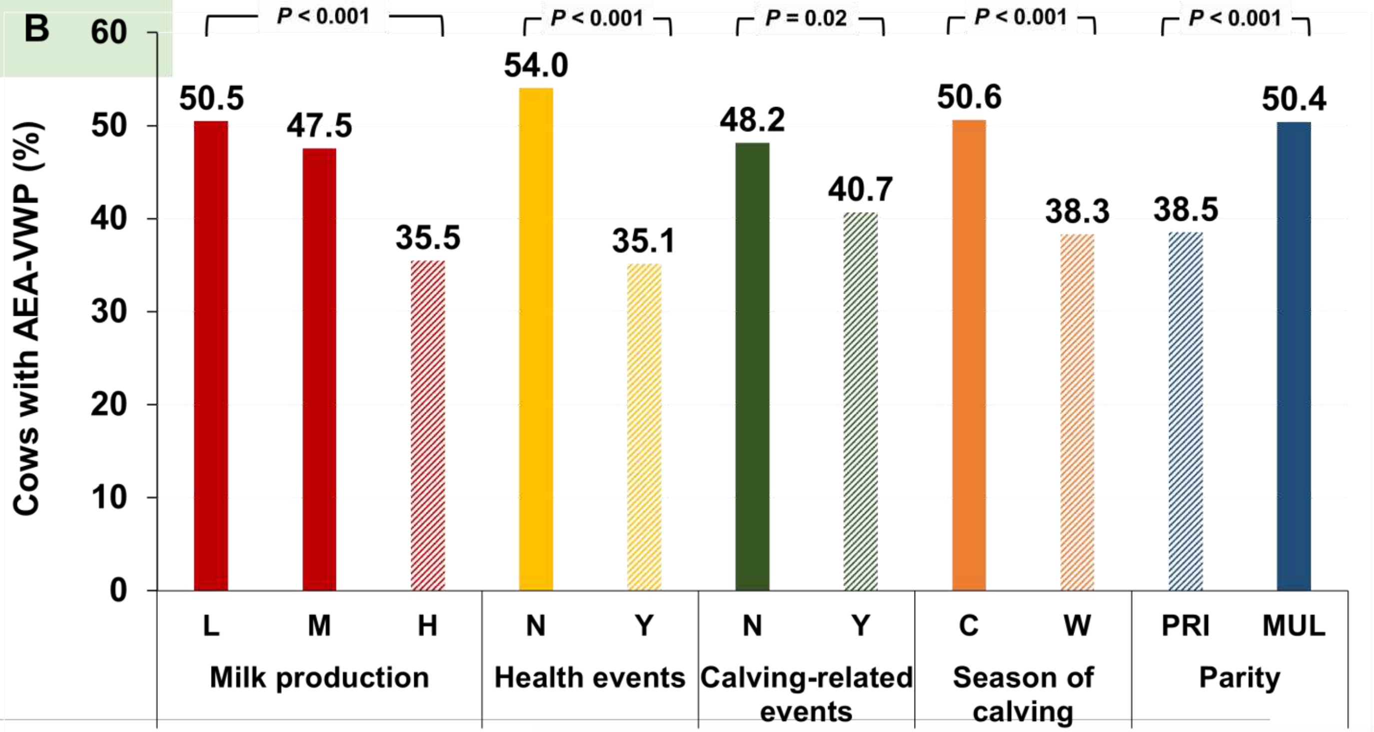
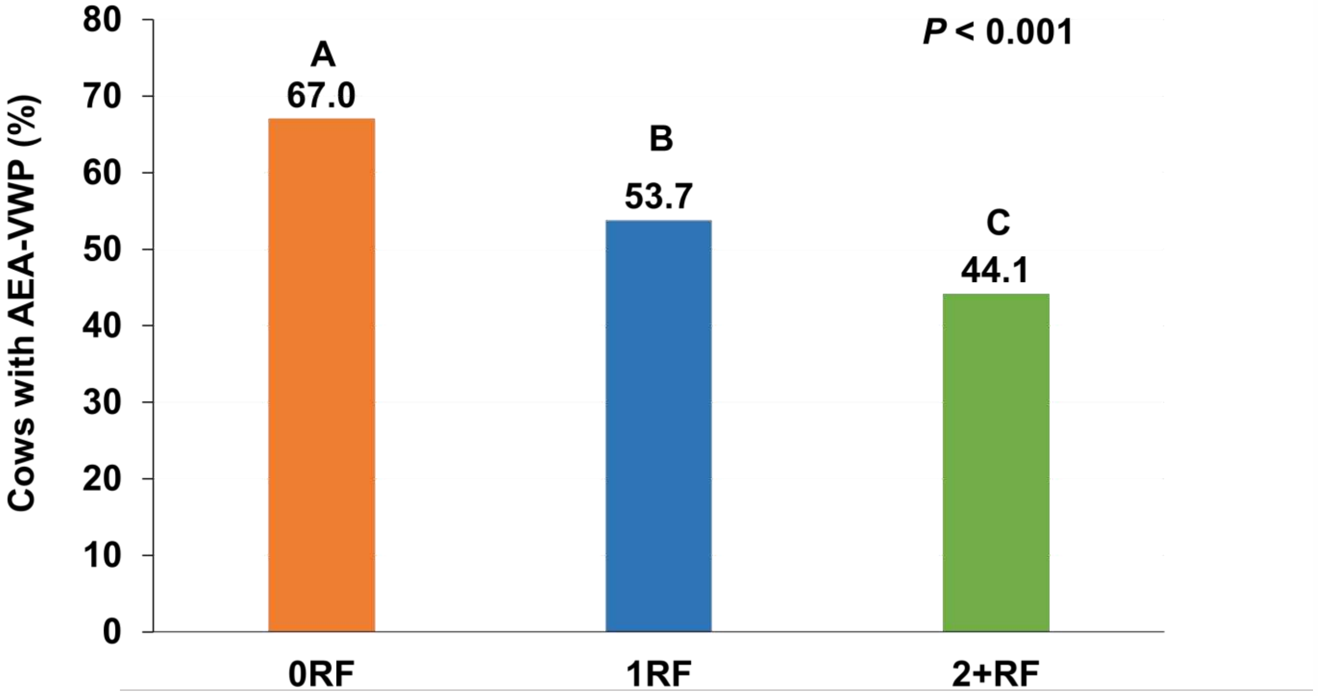
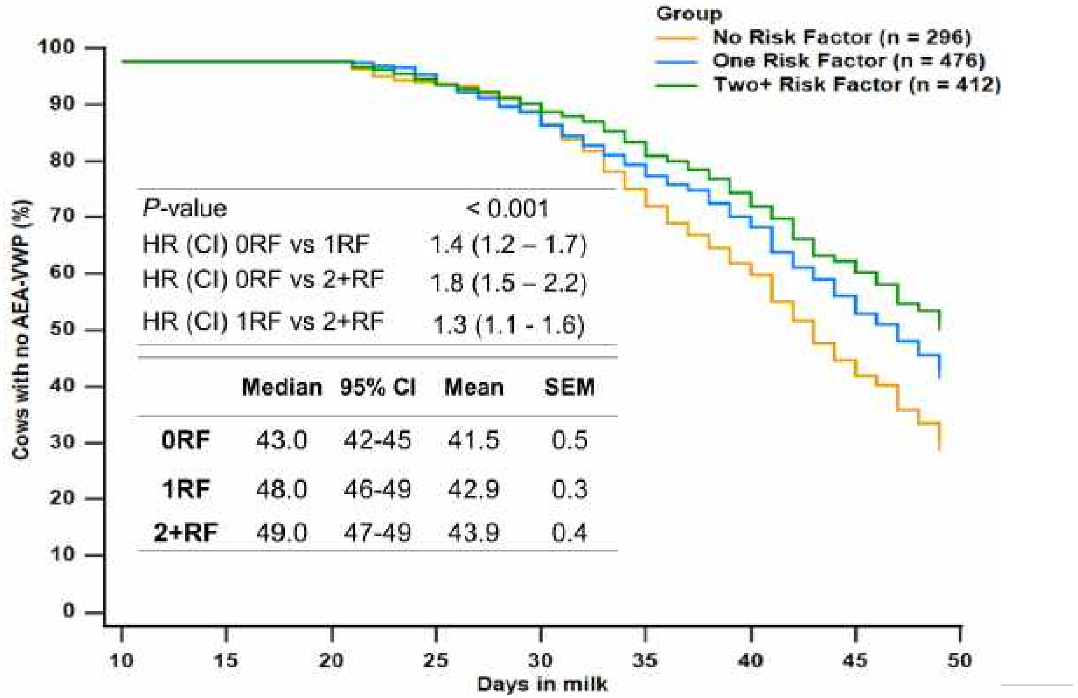

Potential risk factors for estrus expression during VWP
Outcomes
Rumination time
Days in close-up pen
Voluntary waiting period (n = 1,184)
-21 d
Calving
21 DIM
49 DIM
End VWP
Season
Twins
Abortion
Stillbirth
Dystocia
Milk production
gDPR
Health events
Rumination time
Parity
Proportion of cows with AEA during the VWP
Days in milk at first AEA


B
Cows with AEA-VWP (%)
0
10
20
30
40
50
60
P < 0.001
P < 0.001
P = 0.02
P < 0.001
P < 0.001
50.5
47.5
35.5
54.0
35.1
48.2
40.7
50.6
38.3
38.5
50.4
L
M
H
N
Y
N
Y
C
W
PRI
MUL
Milk production
Health events
Calving-related events
Season of calving
Parity

Cows with fewer risk factors were more likely to express estrus and express estrus earlier during the VWP than cow with more risk factors

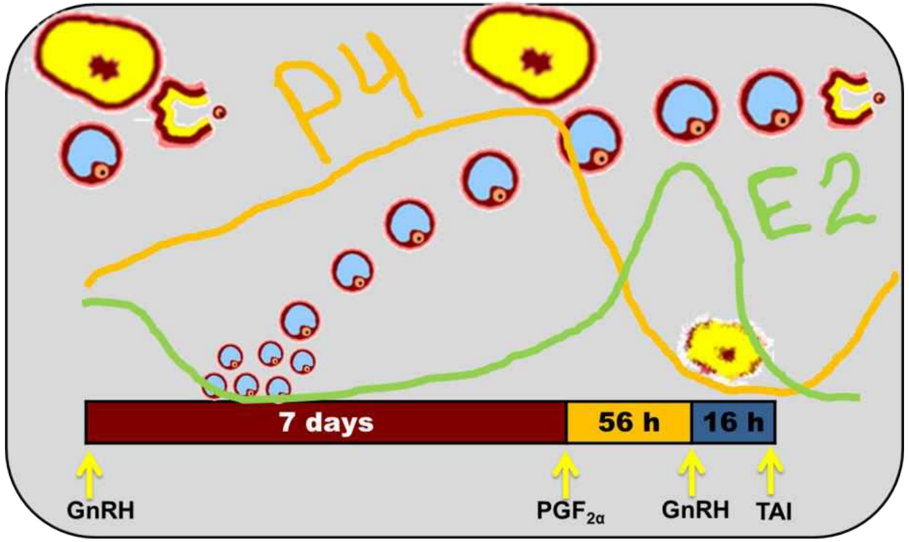
0RF = 25.0% (296/1,184)	1RF = 40.2% (476/1,184)	2+RF = 34.8% (412/1,184)



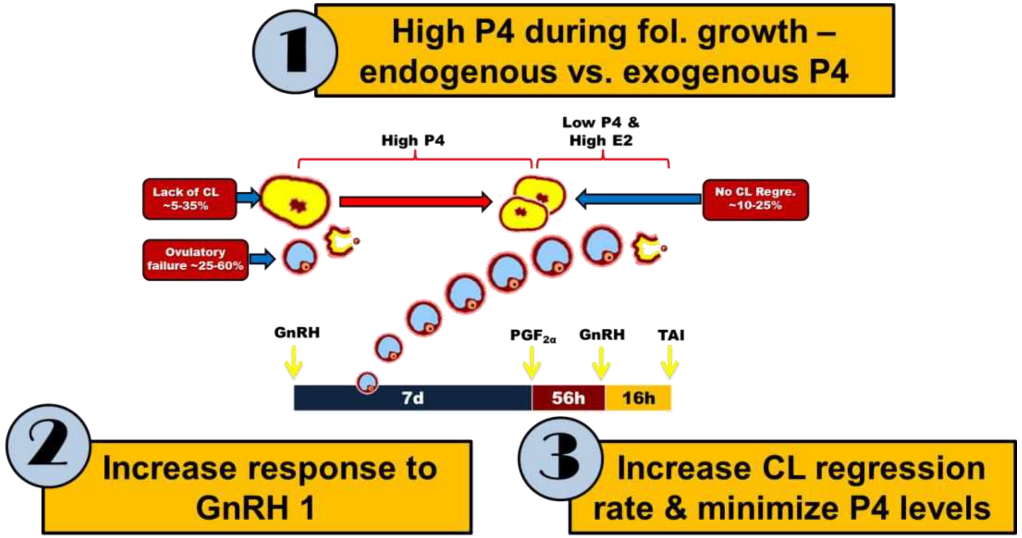


P-value	< 0.001
HR (CI) 0RF vs 1RF	1.4 (1.2 – 1.7)
HR (CI) 0RF vs 2+RF	1.8 (1.5 – 2.2)
HR (CI) 1RF vs 2+RF	1.3 (1.1 - 1.6)

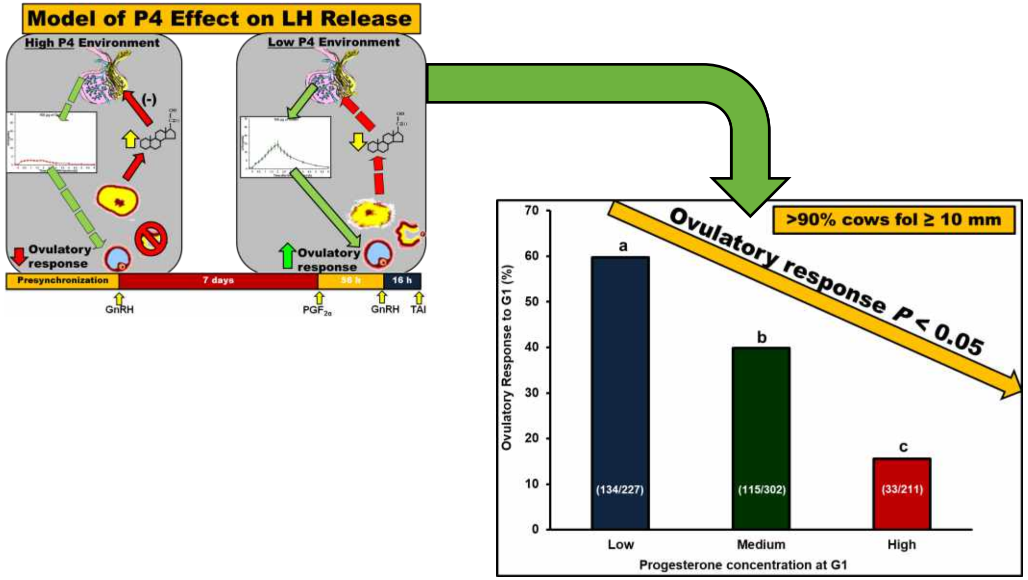
	Median	95% CI	Mean	SEM
0RF	43.0	42-45	41.5	0.5
1RF	48.0	46-49	42.9	0.3
2+RF	49.0	47-49	43.9	0.4



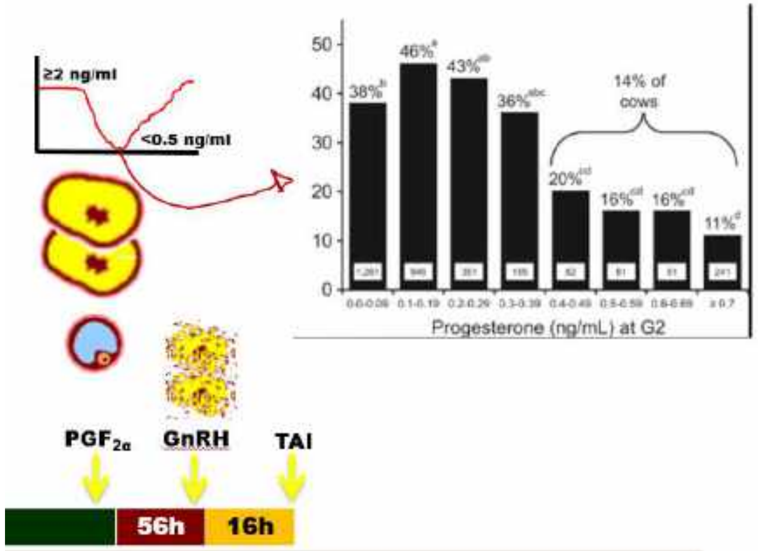
P4
E2
7 days
56 h
16 h
GnRH
PGF2α
GnRH
TAI



1
High P4 during fol. growth – endogenous vs. exogenous P4
High P4
Low P4 & High E2
Lack of CL ~5-35%
No CL Regre. ~10-25%
Ovulatory failure ~25-60%
GnRH
PGF2α
GnRH
TAI
7d
56h
16h
2
Increase response to GnRH 1
3
Increase CL regression rate & minimize P4 levels

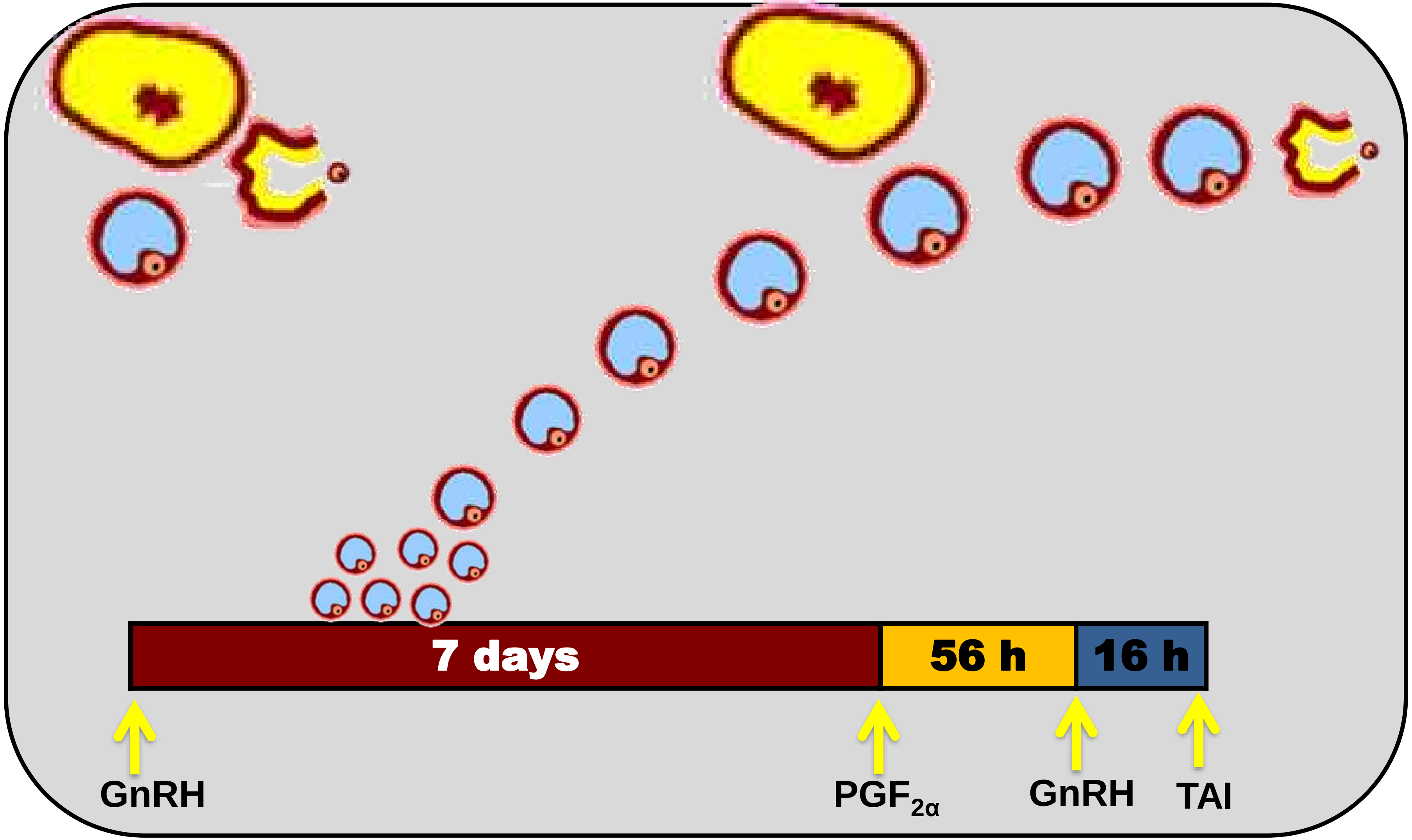


Model of P4 Effect on LH Release
High P4 Environment
Low P4 Environment
(-)
Ovulatory response
Ovulatory response
Presynchronization
7 days
56 h
16 h
GnRH
PGF2α
GnRH
TAI
>90% cows fol ≥ 10 mm
Ovulatory response P < 0.05
Ovulatory Response to G1 (%)
70
60
50
40
30
20
10
0
a
b
c
(134/227)
(115/302)
(33/211)
Low
Medium
High
Progesterone concentration at G1



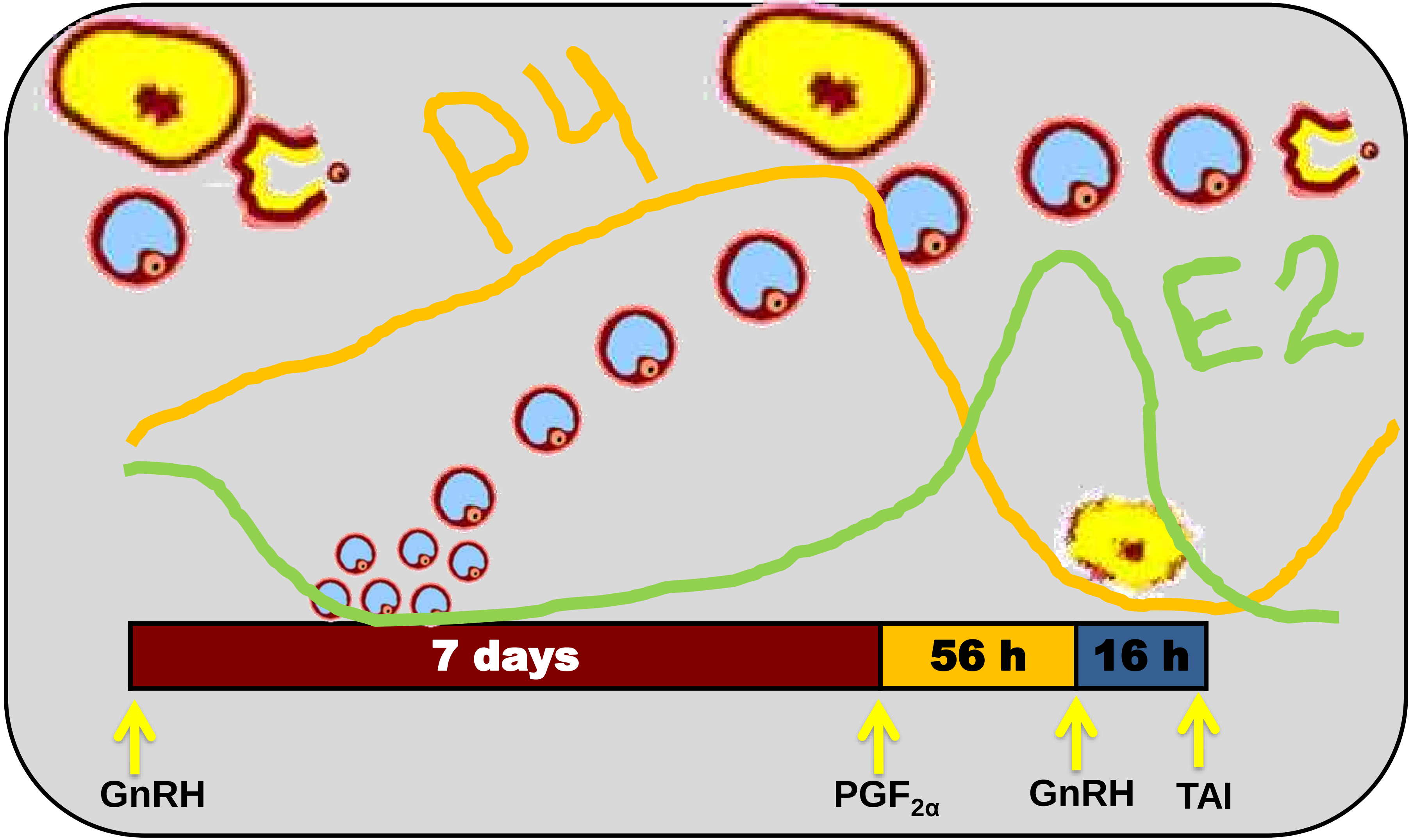
≥2 ng/ml
<0.5 ng/ml
50
40
30
20
10
0
38%
46%
43%
36%
14% of cows
20%
16%
16%
11%
Progesterone (ng/mL) at G2
PGF2α
GnRH
TAI
56h
16h

Ovarian Physiology During Ovsynch



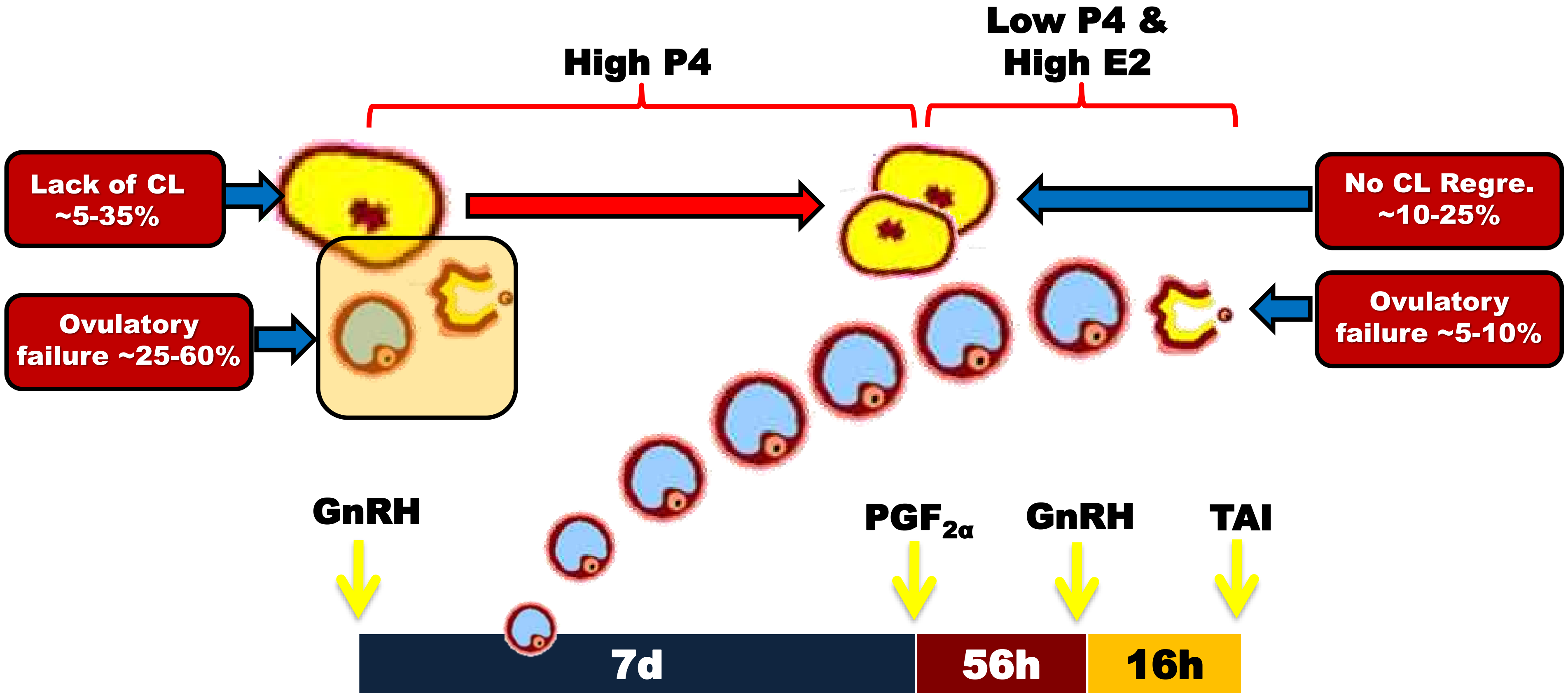
Pursley et al. 1995

Ovarian Physiology During Ovsynch



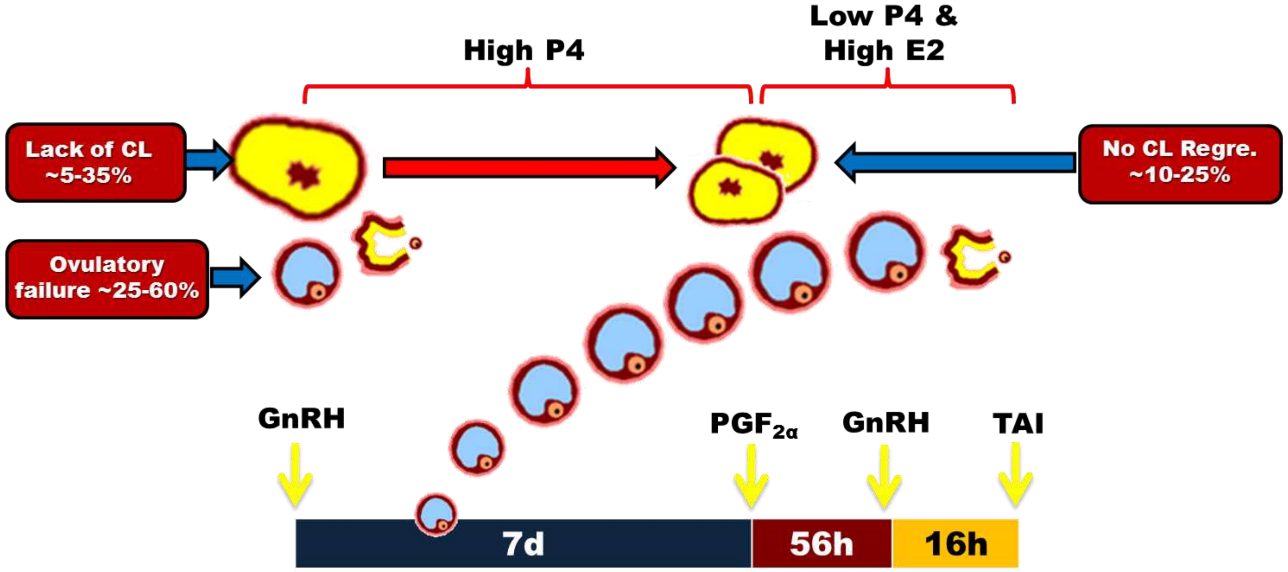
Pursley et al. 1995

Critical steps and associated issues in synchronization protocols



Strategies for optimizing TAI programs

1 High P4 during fol. growth – endogenous vs. exogenous P4

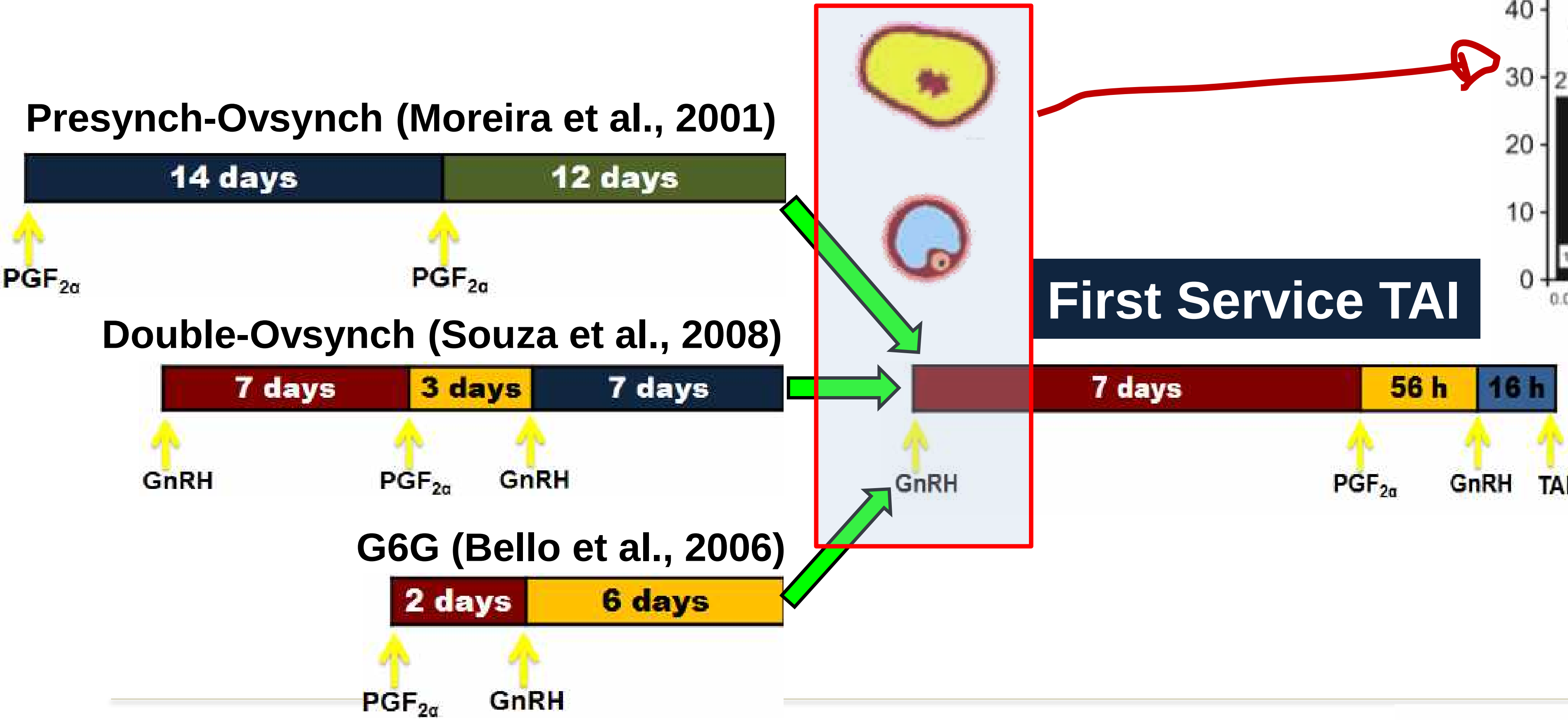


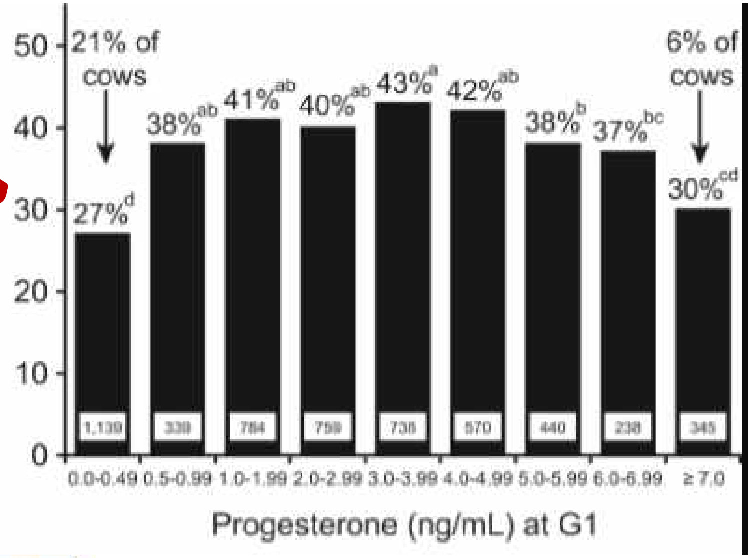
2 Increase response to GnRH 1

3 Increase CL regression rate & minimize P4 levels

Fertility programs include presynchronization of the estrous cycle to optimize P/AI

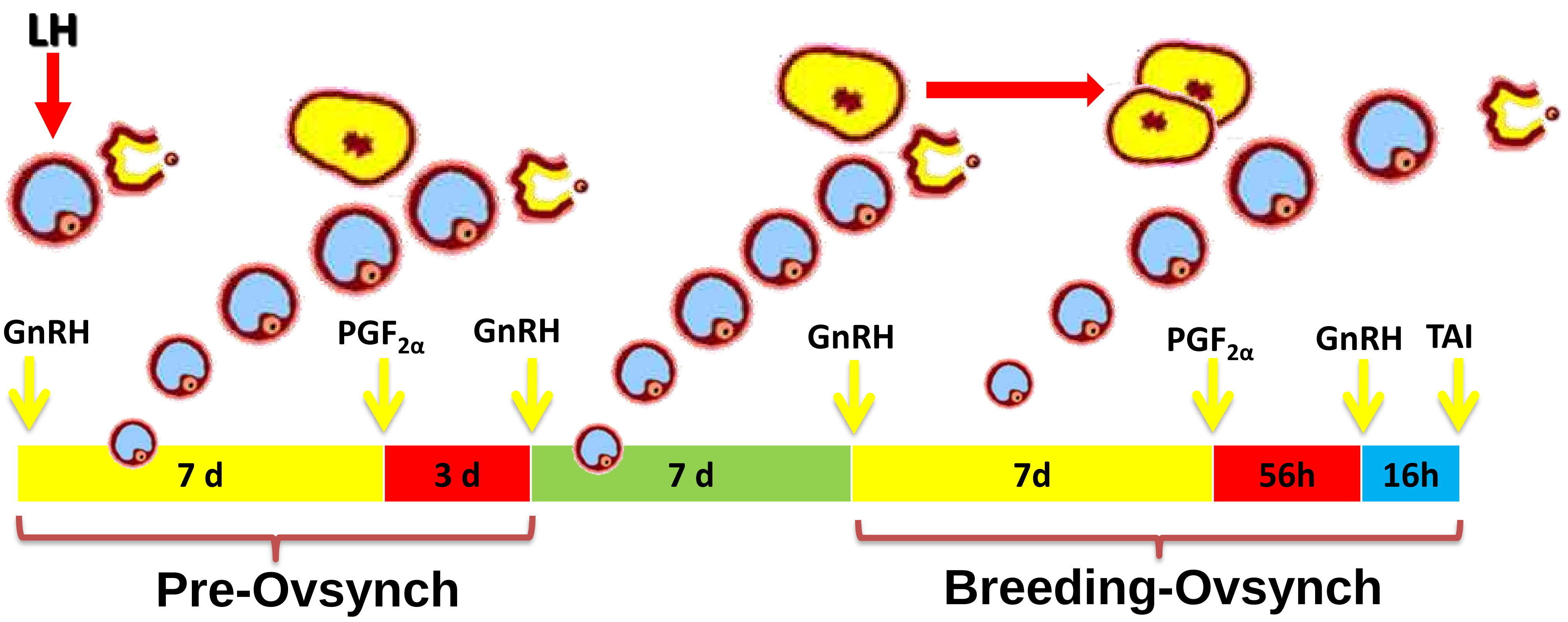
1 High P4 during fol. growth – endogenous vs. exogenous P4





Carvalho et al., 2015

Physiology Double-Ovsynch



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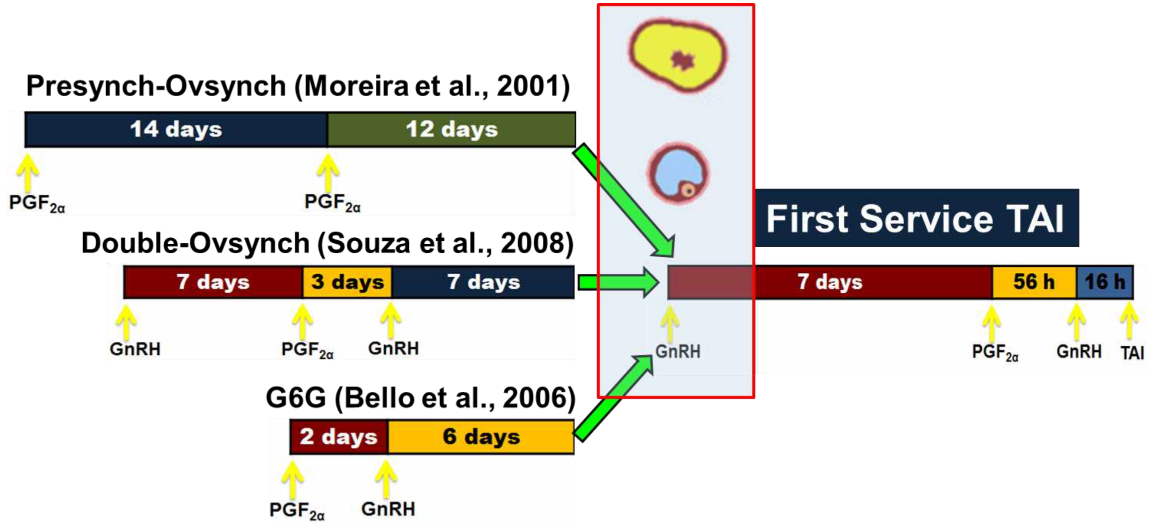
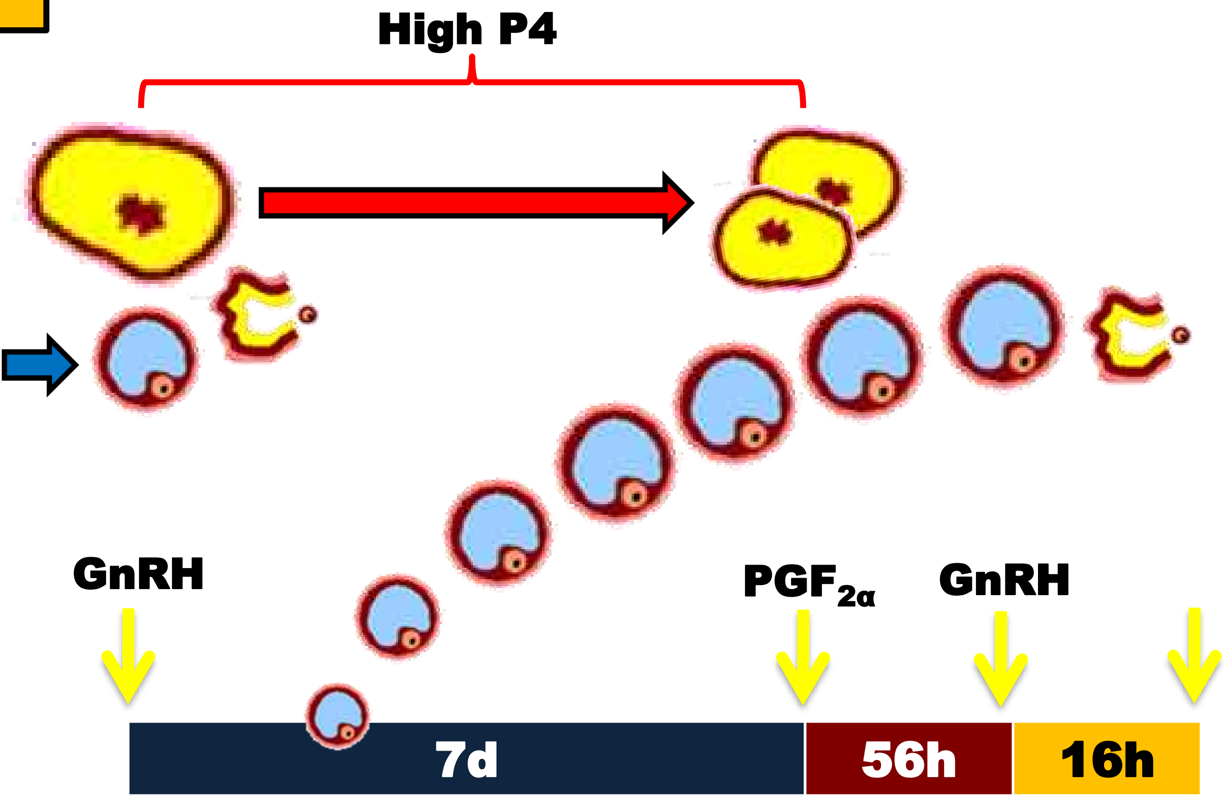
Souza et al., 2008; Giordano et al., 2012; Herlihy et al., 2012; Giordano et al., 2013

Fertility programs include presynchronization of the estrous cycle to optimize P/AI

1 High P4 during fol. growth – endogenous vs. exogenous P4





Fertility programs include presynchronization of the estrous cycle to optimize P/AI

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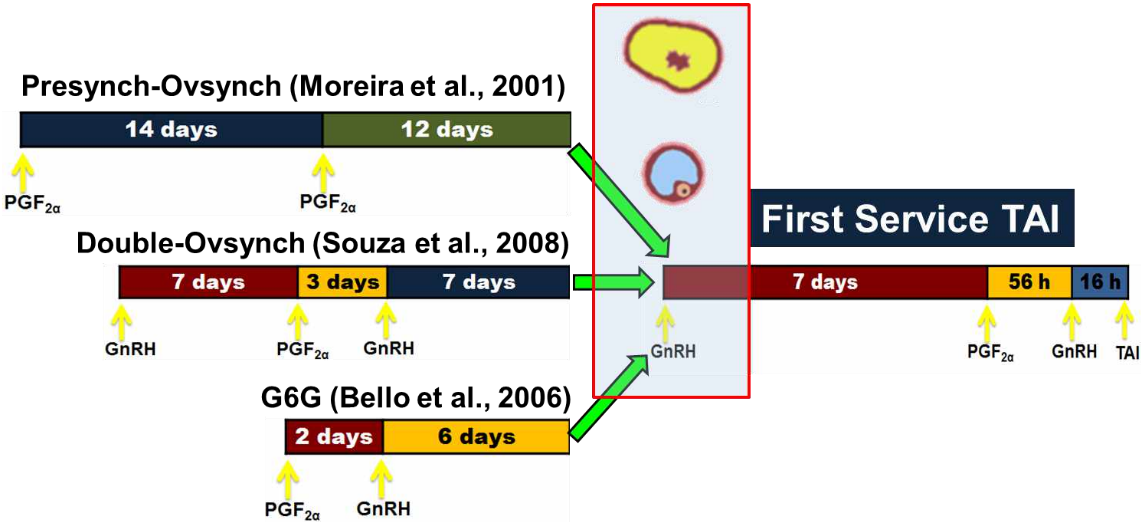
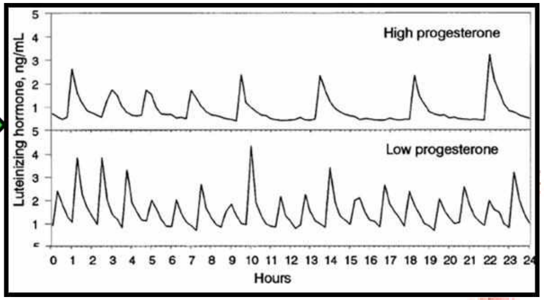
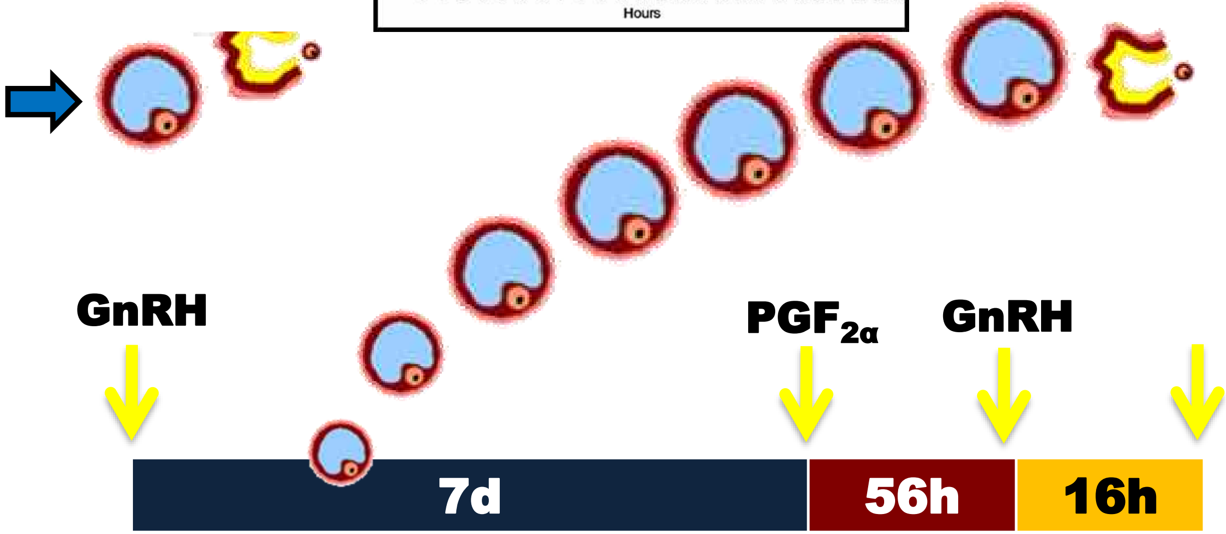


P4 &
LH pulses





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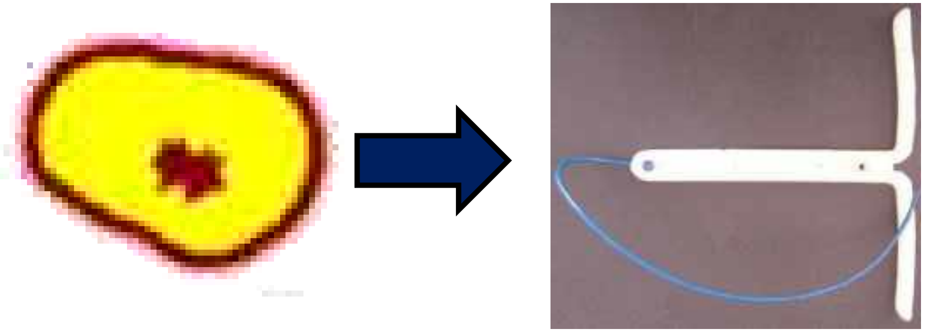
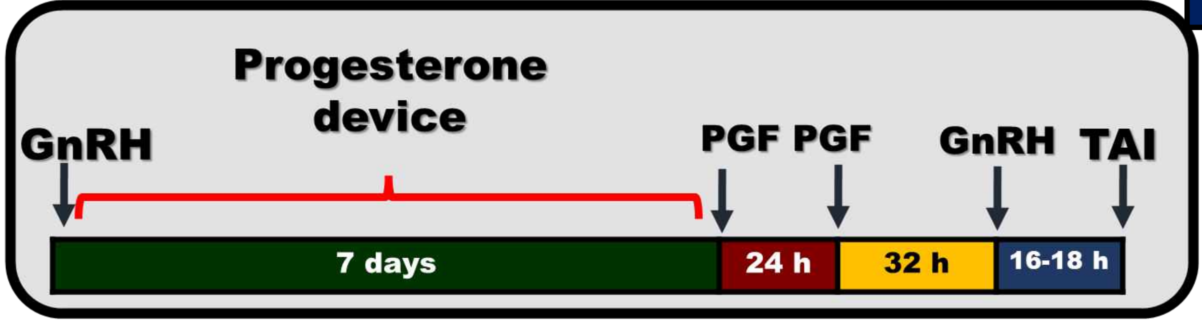
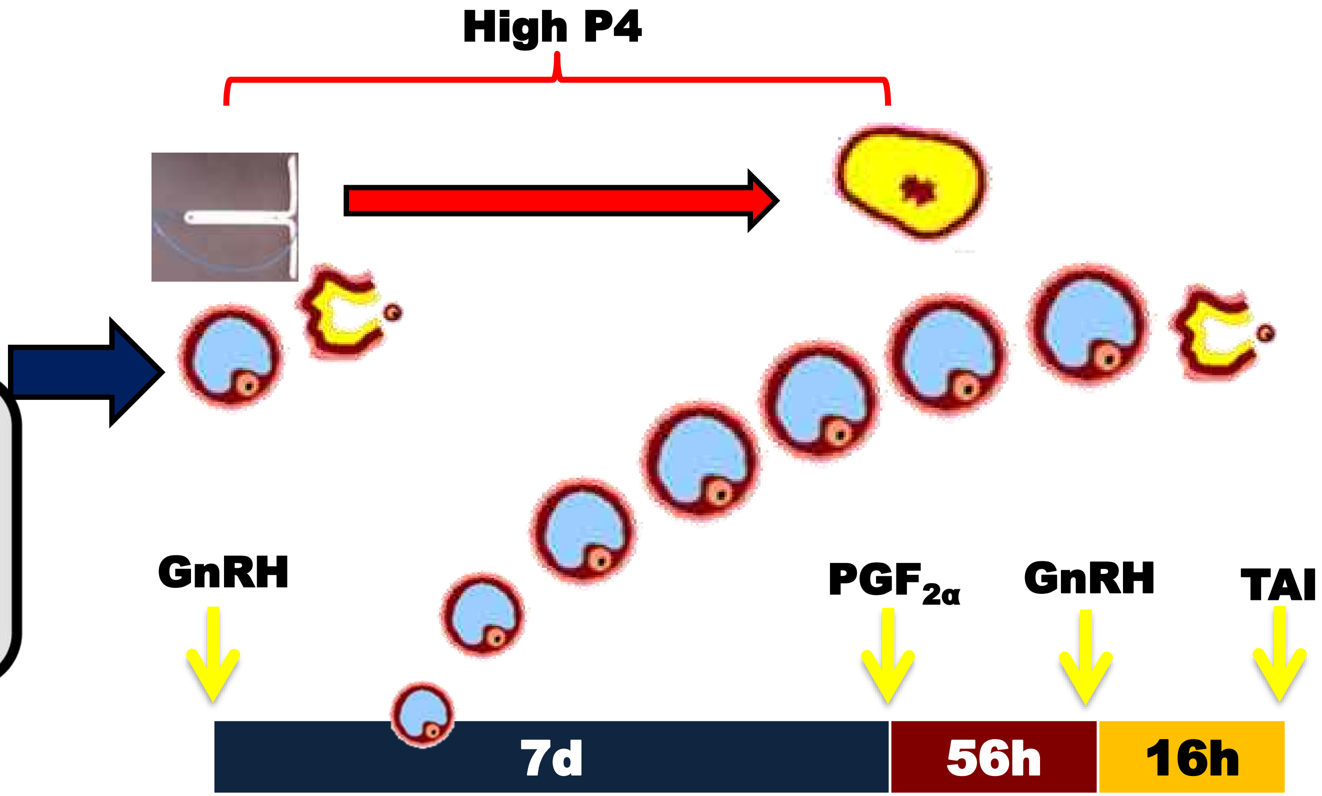
1 High P4 during fol. growth – endogenous vs. exogenous P4







Fertility programs include presynchronization of the estrous cycle to optimize P/AI

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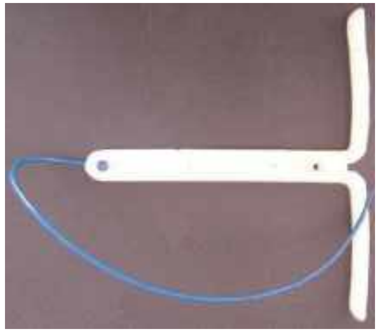
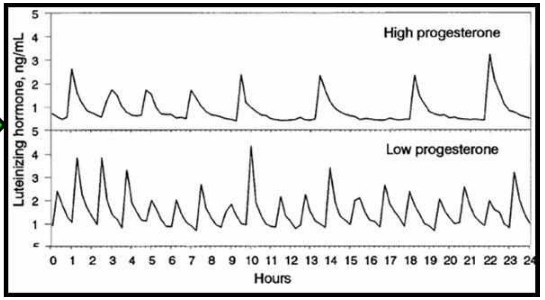
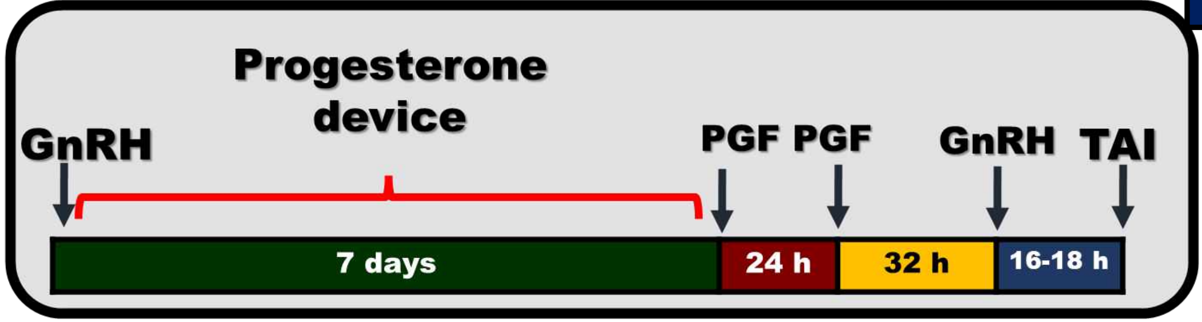
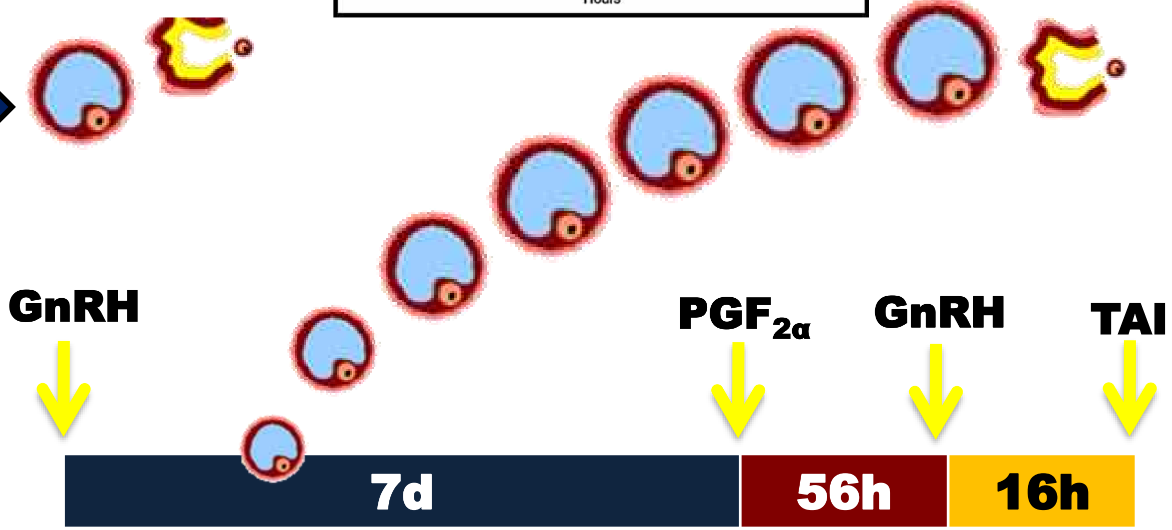


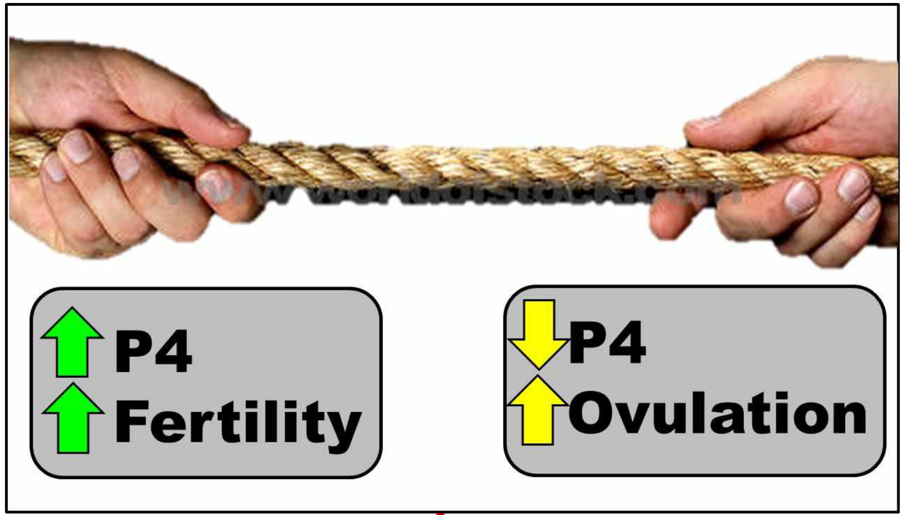
P4 & LH pulses

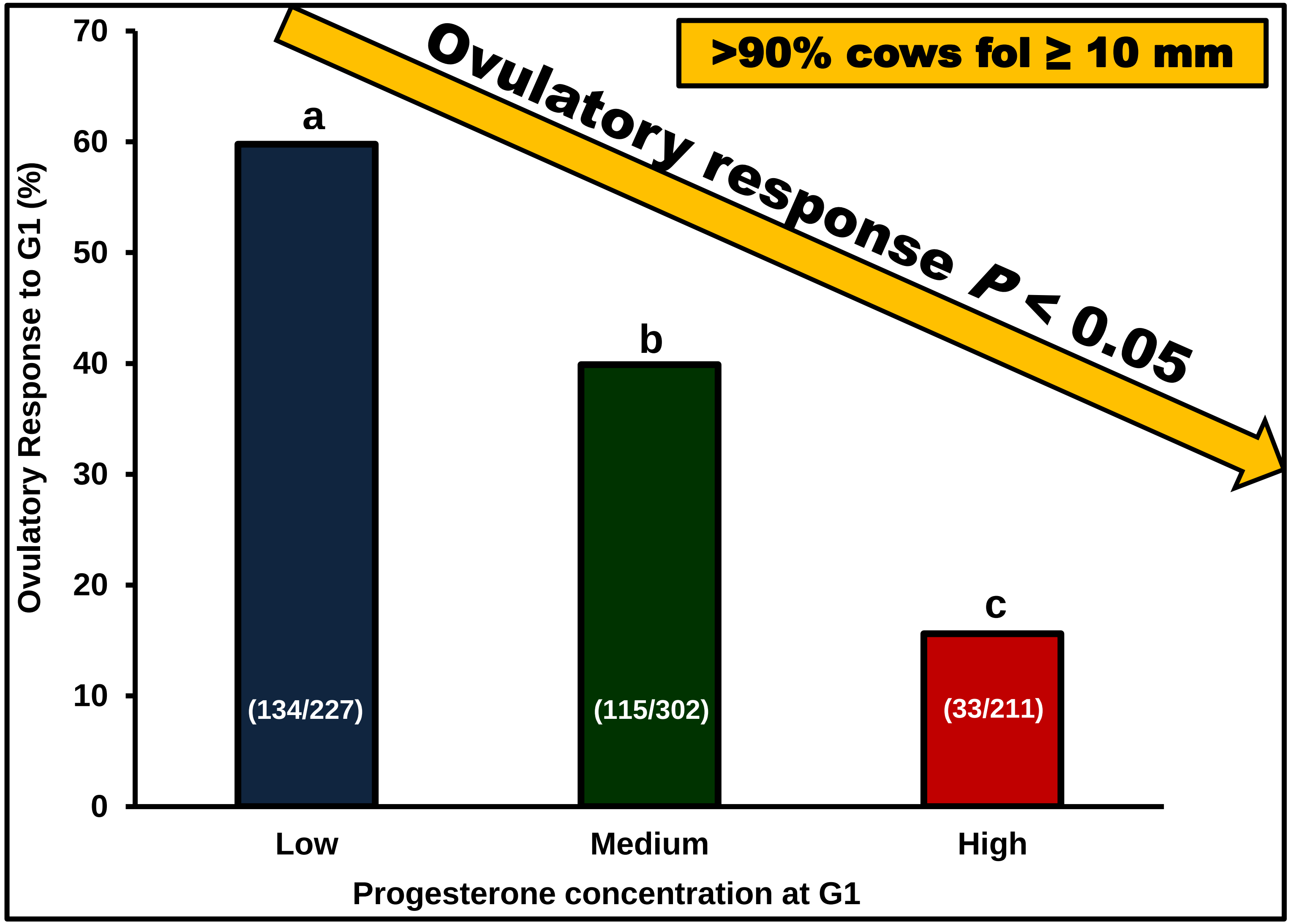






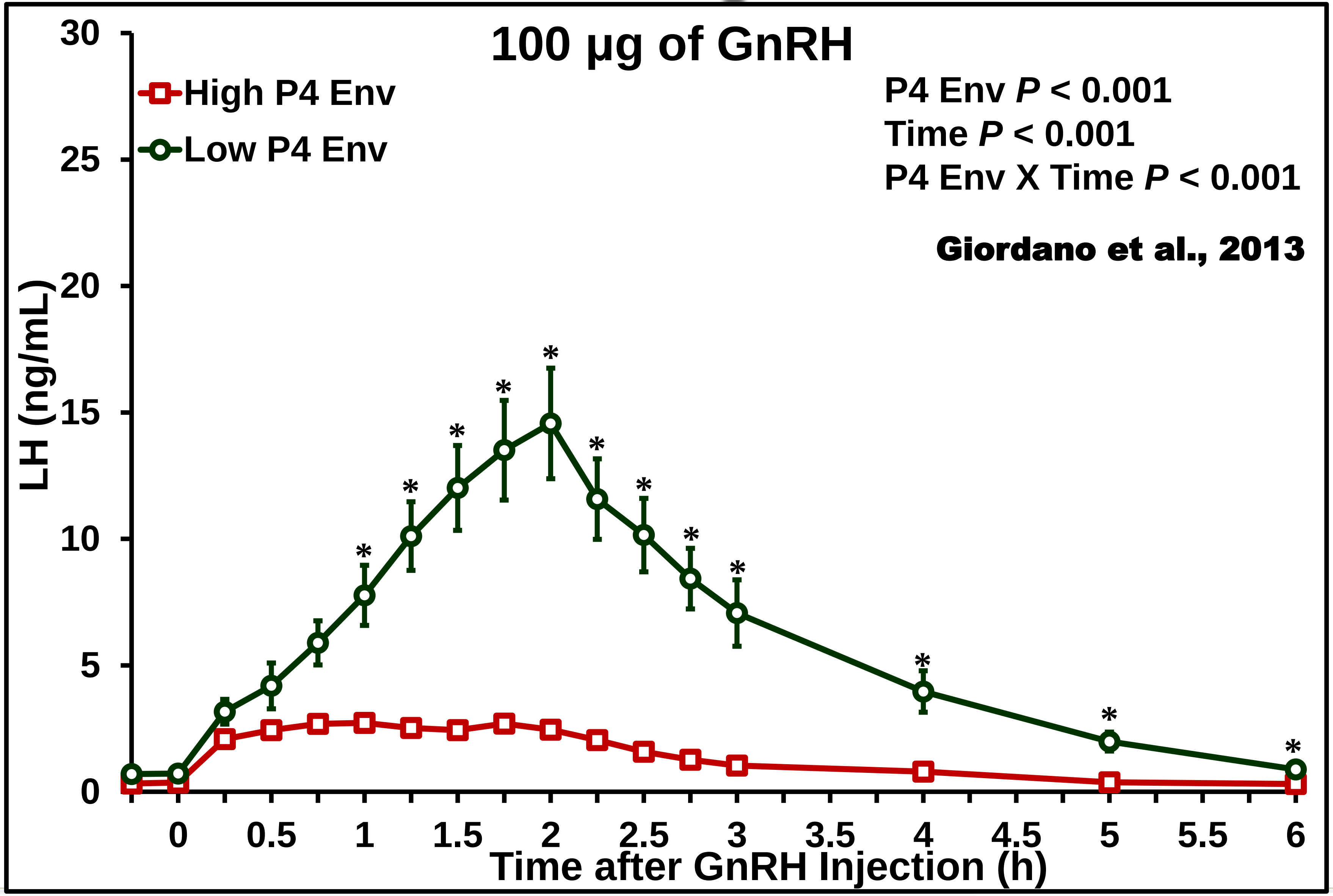
P4 levels affect ovulatory response to GnRH



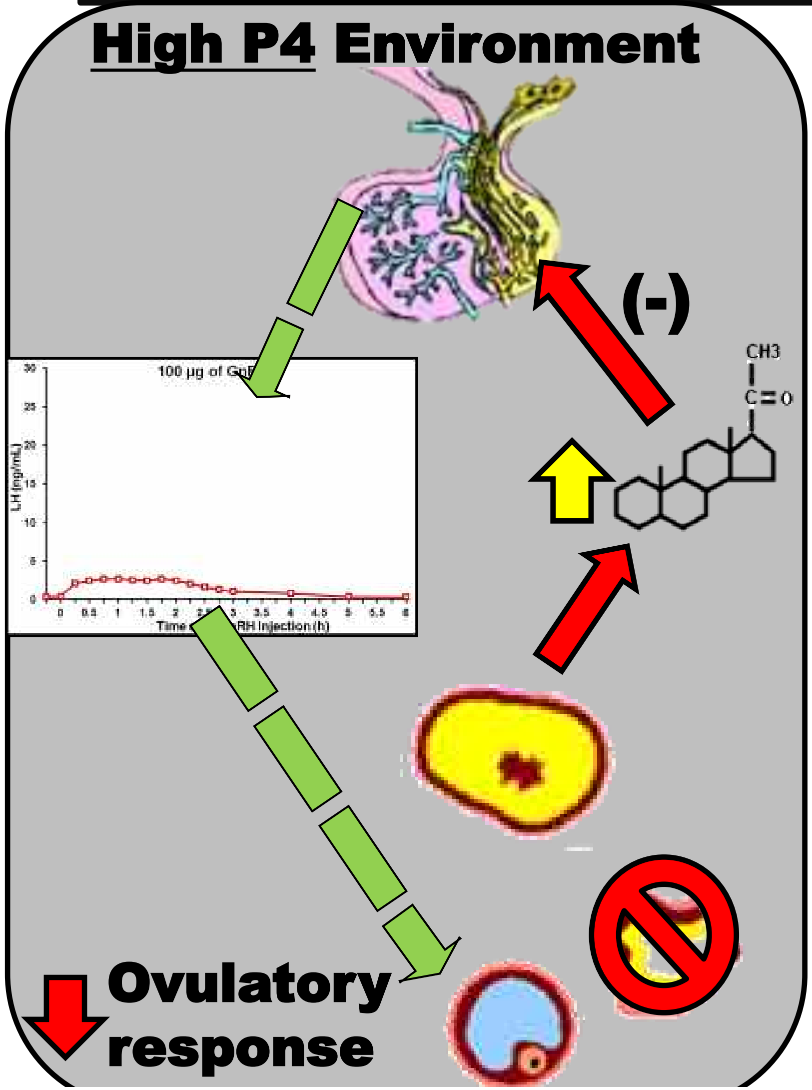


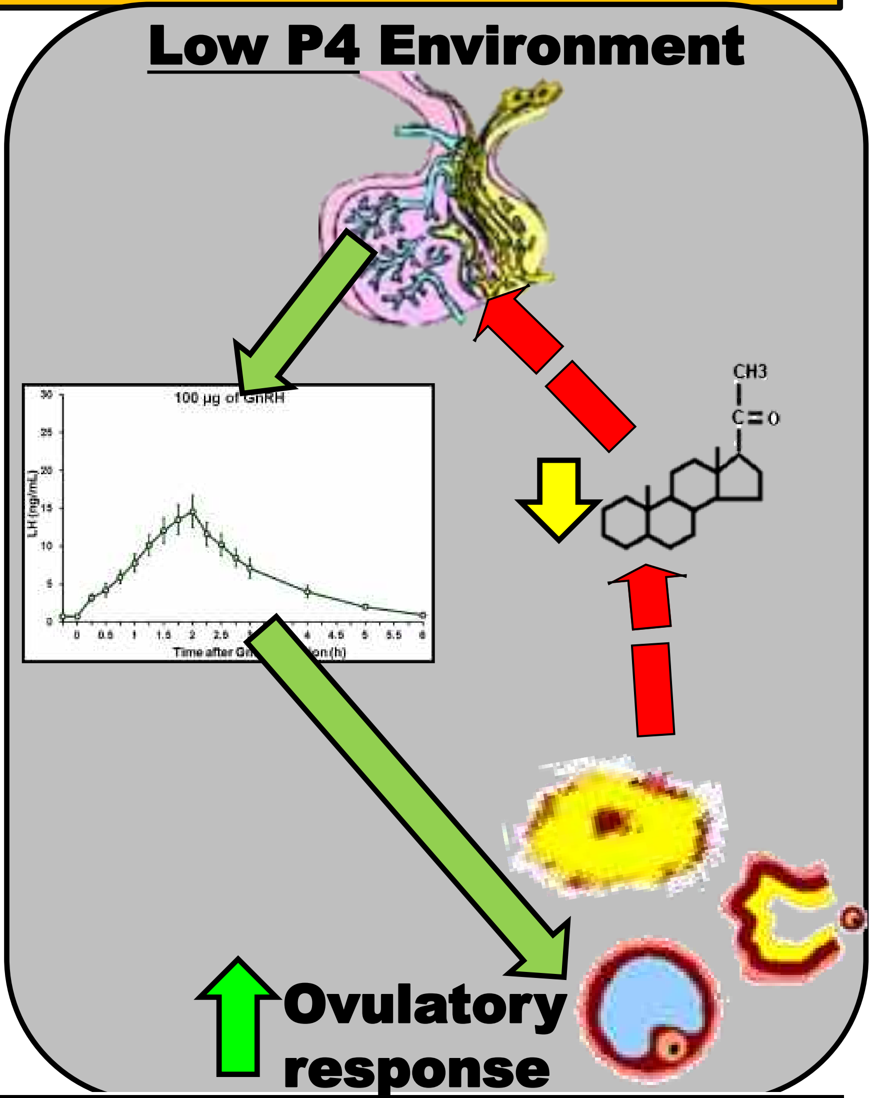
Giordano et al., 2013

Effect of P4 on LH response to GnRH



Model of P4 effect on LH release





Presynchronization	7 days	56 h	16 h

GnRH PGF$_{2\alpha}$ GnRH TAI

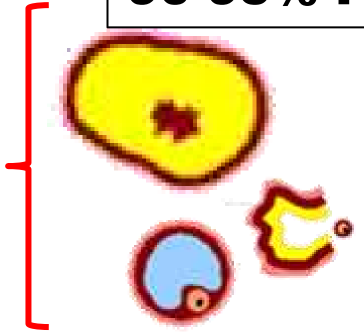
Strategies for optimizing ovulatory response to 1st GnRH

2

Increase response to GnRH 1

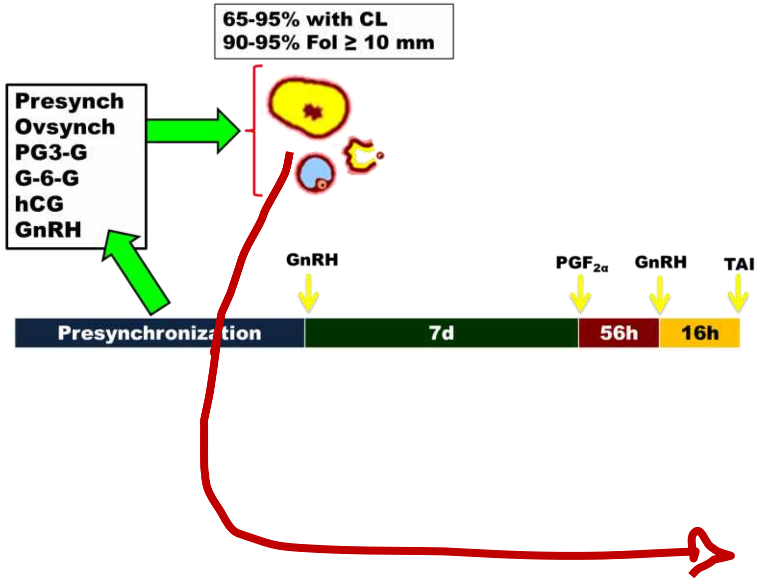
- Presynch
- Ovsynch
- PG3-G
- G-6-G
- hCG
- GnRH

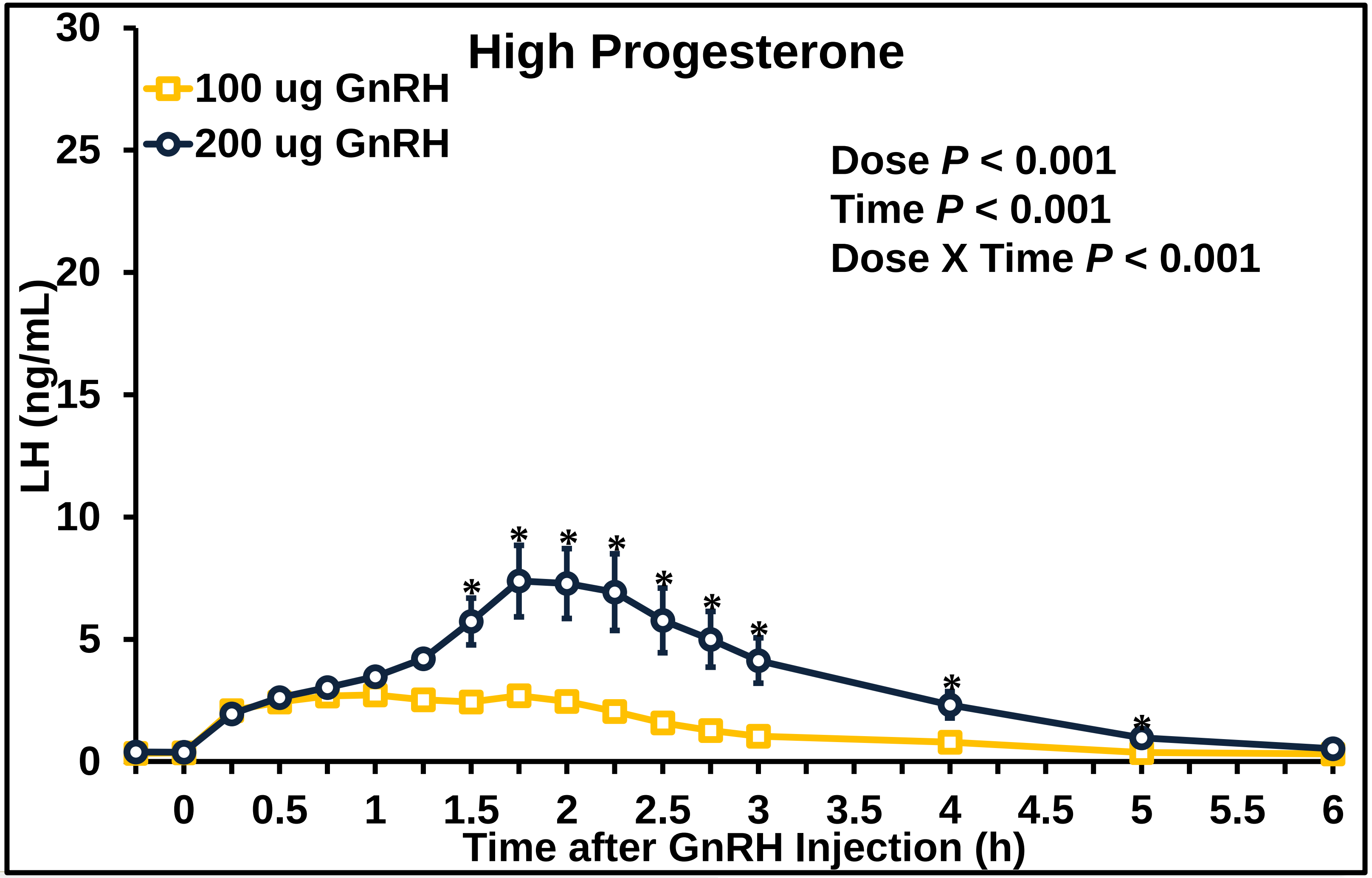
65-95% with CL
90-95% Fol ≥ 10 mm



- -Greater GnRH dose
- -Induce partial CL regression
- -hCG?

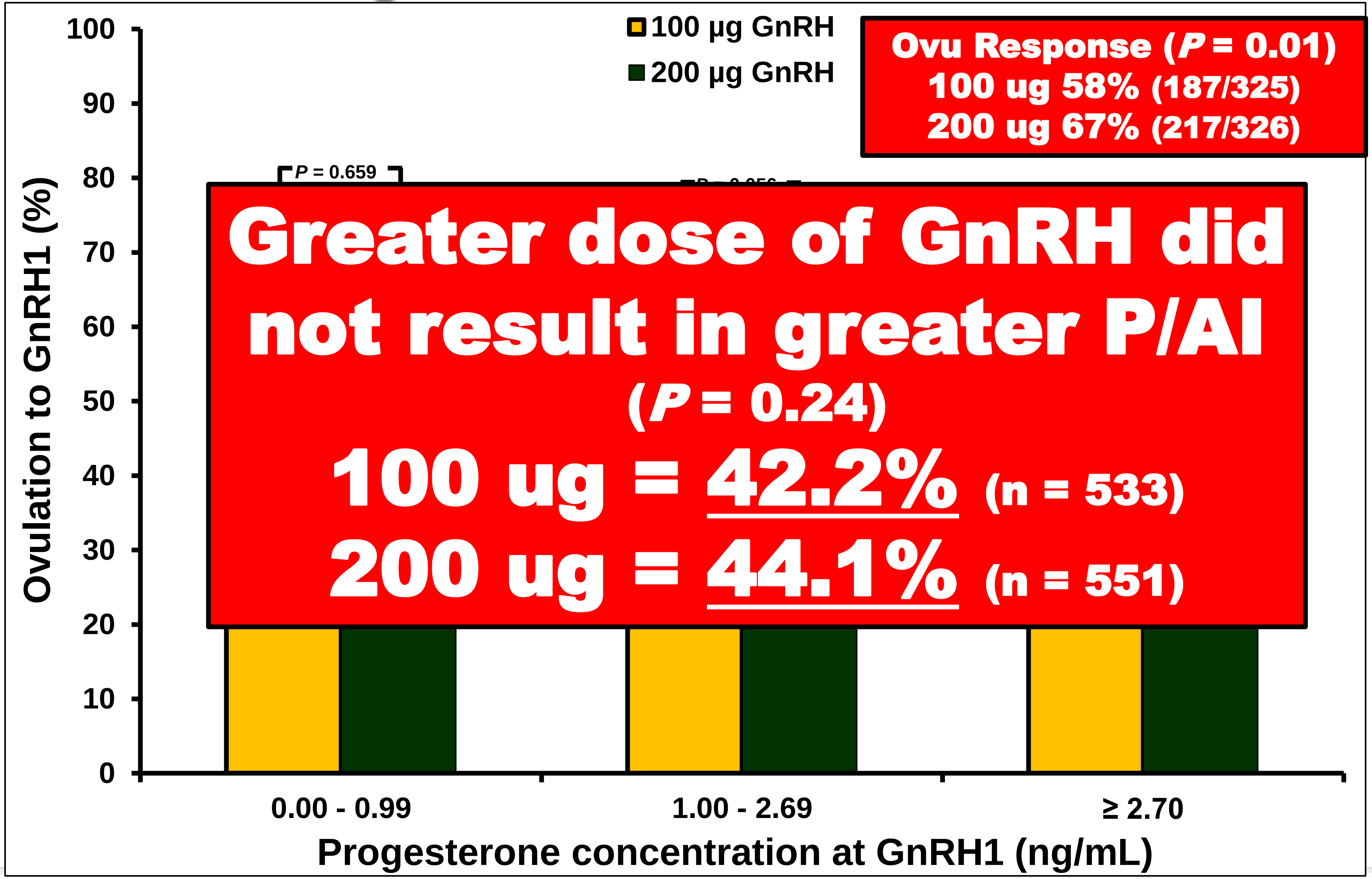
Greater doses of GnRH increased GnRH-induced LH surge





Giordano et al., 2013

Greater GnRH dose increased ovulation in a P4 concentration dependent manner

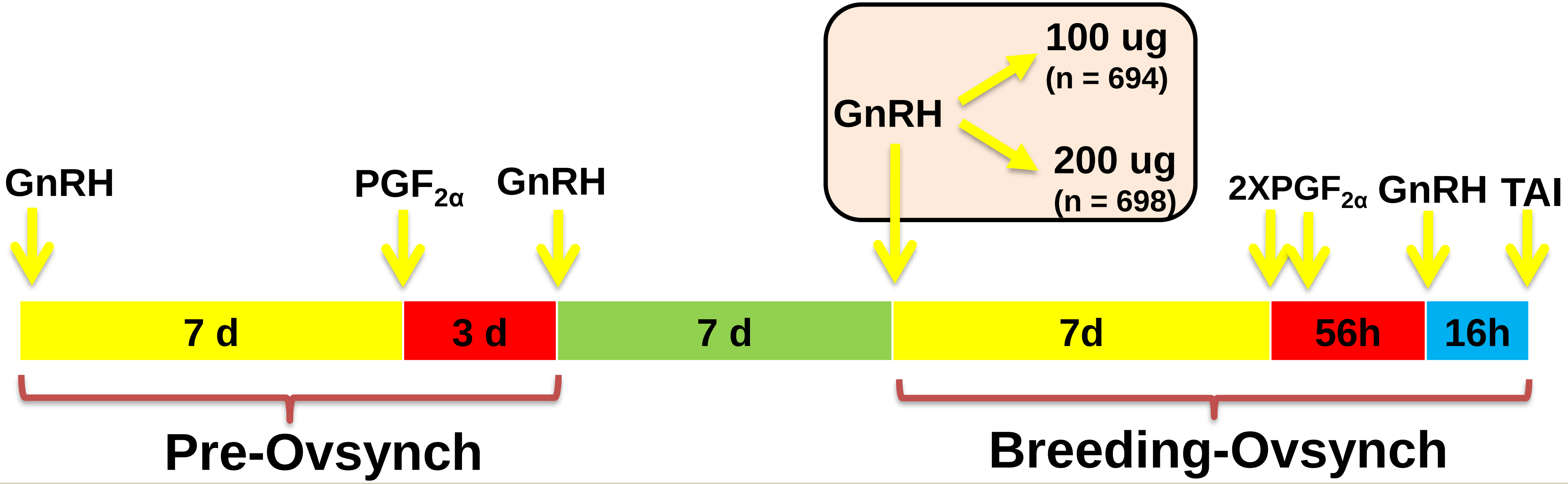


Giordano et al., 2013

Explored effect of GnRH dose on fertility to TAI

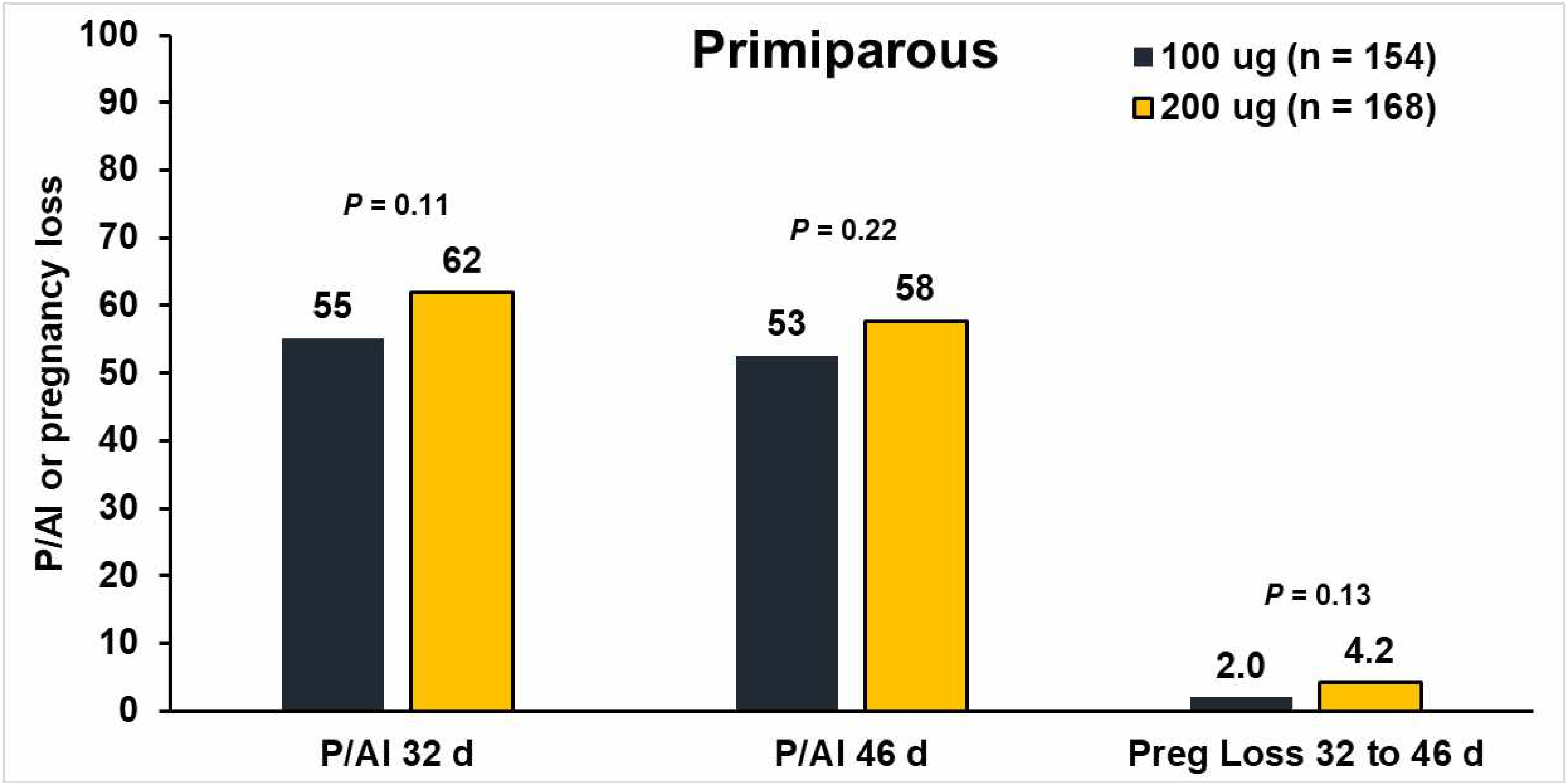
242 **Effect of a high dose of gonadorelin hydrochloride at the first gonadotropin-releasing hormone of the breeding-Ovsynch of a fertility program on ovulation rate and pregnancies per AI in first-service lactating Holstein cows.** T. Valdes Arciniega*[1], I. M. R. Leão[1], E. Anta Galvan[1], T. O. Cunha[1], M. S. El Azzi[1,2], N. B. Cook[1], and J. P. N. Martins[1], [1]*School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI,* [2]*Universidade Federal de Lavras, Lavras, MG, Brazil.*

- CRD to evaluate effect of 100 vs 200 ug of **Gonadorelin hydrochloride**
- Lactating Holstein cows – 1st TAI at 64-75 primi (n = 720), 59-70 multi (n = 1,192)
- Conventional semen only



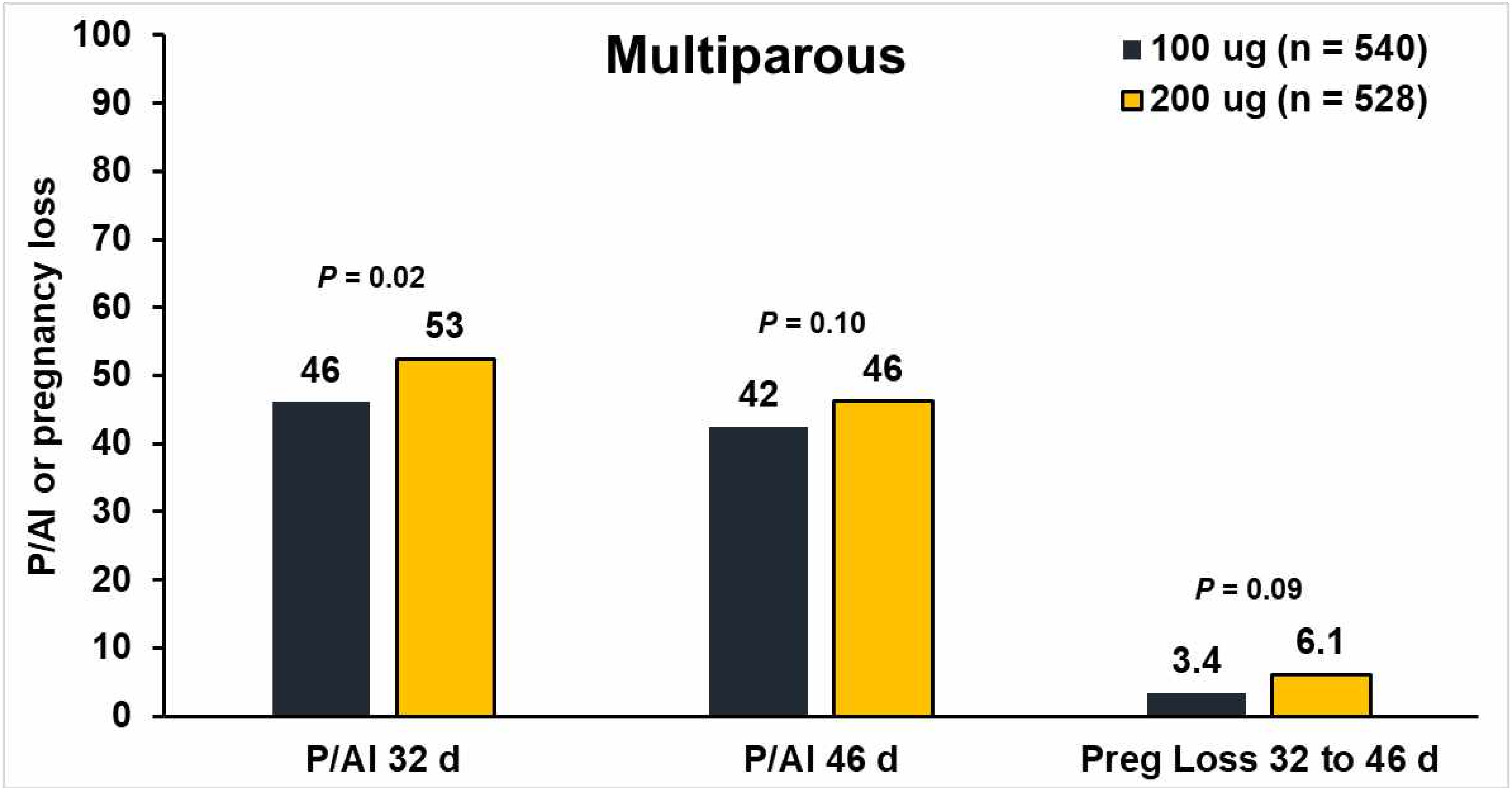
Valdes-Arciniega et al., 2020 (JDS Abstract)

Effect of GnRH (Gonadorelin hydrochloride) dose on P/AI - Primiparous cows



Valdes-Arciniega et al., 2020 (JDS Abstract)

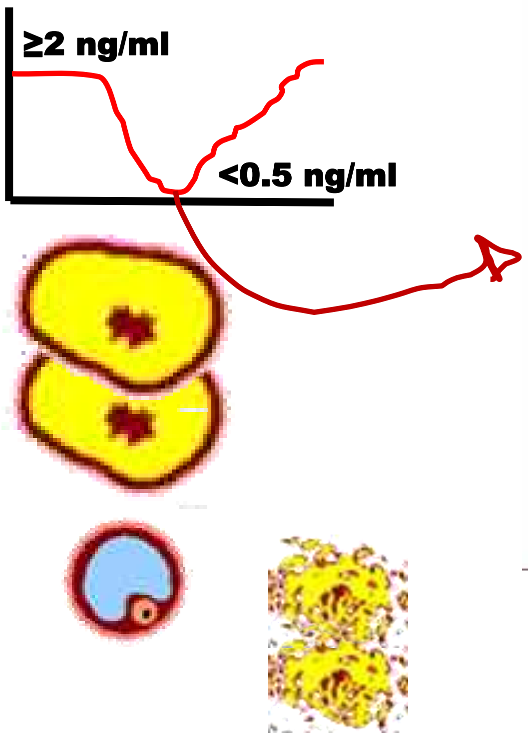
Effect of GnRH (Gonadorelin hydrochloride) dose on P/AI – Multiparous cows

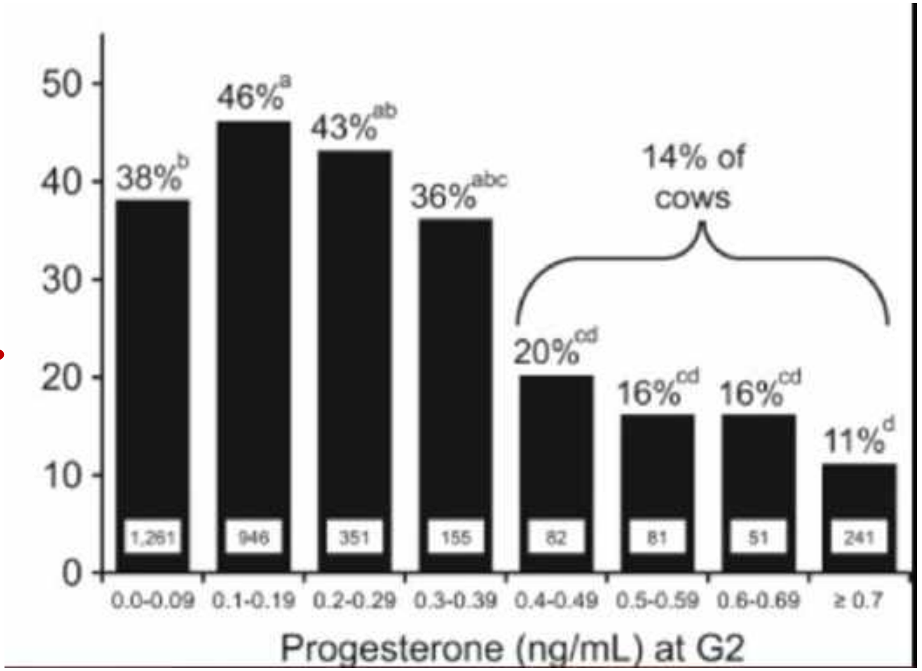


Valdes-Arciniega et al., 2020 (JDS Abstract)

Optimizing luteolysis before TAI increases fertility

3 Increase CL regression rate & minimize P4 levels

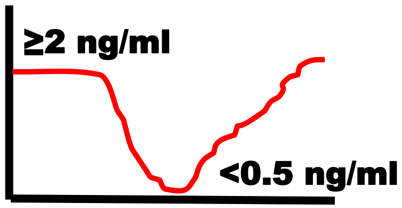


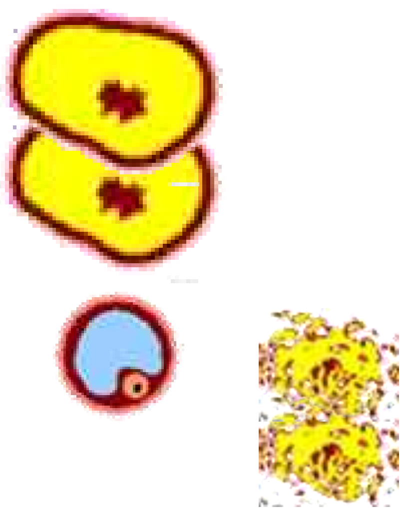


Type of CL present at induction of luteolysis affects the response to PGF

Type of CL presents affects response to PGF

-Greater PGF dose
-Sequential PGF treatments





Item	Group			P-value
	Old CL	Old+New CL	New CL only	
CL regression (<1 ng/mL)	91^{a} (47)	97^{a} (48)	81^{b} (73)	0.04

Sequential PGF treatments (two/24 h) increased CL regression risk

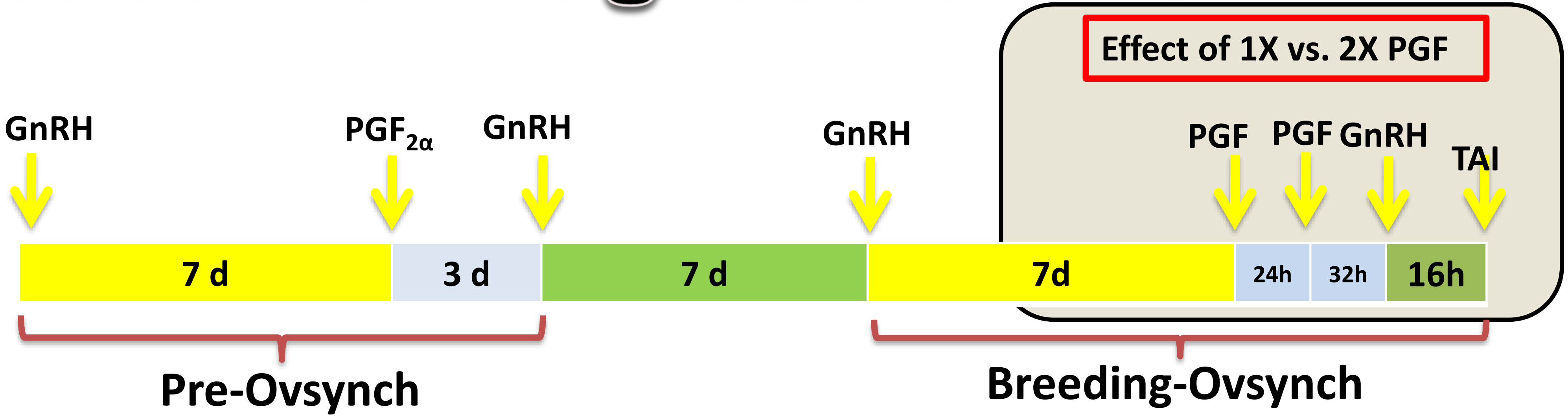


Table 1. Effect of 1 versus 2 treatments with prostaglandin $F_{2\alpha}$ (PGF) on percentage of cows with complete regression of the corpus luteum in primiparous and multiparous cows synchronized with Double-Ovsynch (experiment 1)

% of cows with complete CL regression[1] (no./no.)	1 PGF	2 PGF	*P*-value
Primiparous	81.2 (65/80)	97.5 (77/79)	0.001
Multiparous	84.4 (81/96)	96.7 (86/89)	0.006
P-value	0.69	1.0	
Overall	83.0 (146/176)	97.0 (163/168)	0.0001

[1]Circulating progesterone <0.5 ng/mL at 56 h after first PGF in cows that had ≥2.0 ng/mL of progesterone on the day of first PGF.

2X vs 1X PGF increased CL reg. ~14p.p.

Cornell CALS College of Agriculture and Life Sciences

Wiltbank et al., 2015

Sequential PGF treatments (two/24 h) increased P/AI

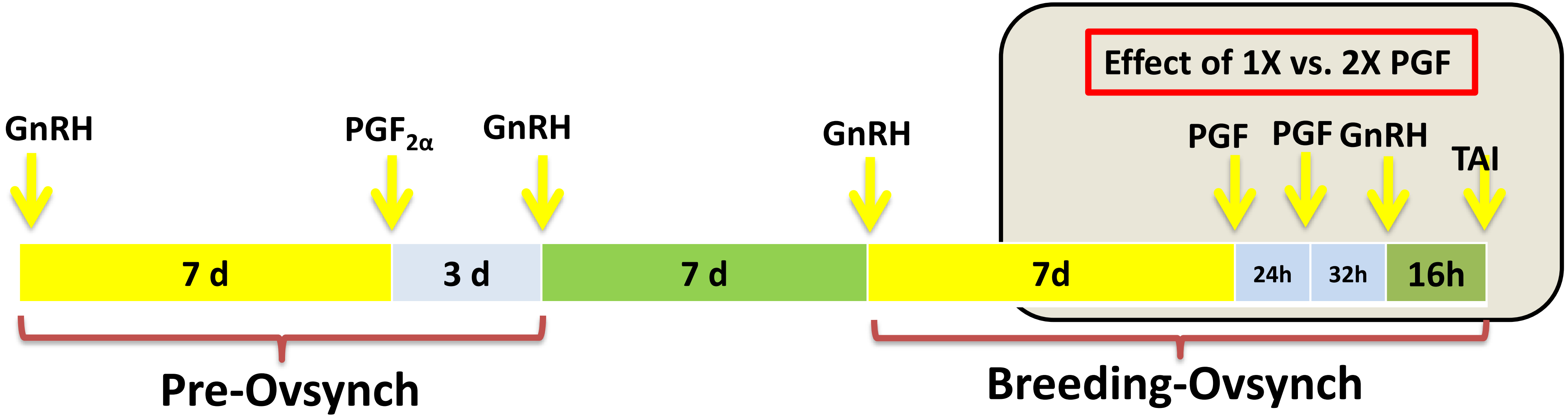


Table 6. Effect of treatment with a second prostaglandin $F_{2\alpha}$ (PGF) on P/AI during the Ovsynch (experiment 2) or Double-Ovsynch (experiment 1) protocols[1]

Parity	1 PGF, % (no./no.)	2 PGF, % (no./no.)	Effect of PGF difference, % (*P*-value)
Primiparous	39.3 (140/356)	40.6 (139/342)	+ 3.31% (0.39)
Multiparous	32.5 (296/910)	36.5 (333/913)	+12.31% (0.043)
P-value	0.04	0.17	
Overall	34.4 (436/1266)	37.6 (471/1251)	+9.45% (0.049)

[1]Results from experiments 1 and 2 were combined for the analysis with all cows assigned to the experiments included in the analysis.

2X vs 1X PGF increased P/AI 4.0 p.p. multiparous only

Cornell CALS College of Agriculture and Life Sciences

Wiltbank et al., 2015

Sequential PGF treatm. (two/24 h) increased CL regression rate

J. Dairy Sci. 101:8566–8571
https://doi.org/10.3168/jds.2017-14191

Short communication: **Effect of adding a second prostaglandin $F_{2\alpha}$ injection during the Ovsynch protocol on luteal regression and fertility in lactating dairy cows: A meta-analysis**

S. Borchardt,* A. Pohl,* P. D. Carvalho,† P. M. Fricke,† and W. Heuwieser*[1]
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Table 2. Effect of an additional treatment with $PGF_{2\alpha}$ during the Ovsynch protocol (n = 1,856) on luteal regression at the end of the protocol considering 6 manuscripts with a randomized controlled study design

Manuscript[1]	Luteal regression 1PGF	Luteal regression 2PGF	Relative risk[2]	95% CI	*P*-value
Barletta et al. (2018)	112/128	133/142	1.07	0.99–1.16	
Brusveen et al. (2009)	151/178	155/162	1.13	1.05–1.21	
Carvalho et al. (2015a)	262/312	281/288	1.16	1.10–1.22	
Heidari et al. (2017)	28/50	35/50	1.25	0.92–1.70	
Santos et al. (2016)	89/100	100/102	1.10	1.02–1.19	
Wiltbank et al. (2015)	146/176	163/168	1.17	1.09–1.26	
$I^2 = 0.00\%$ ($P = 0.450$)					
Total (fixed effects)	788/944	867/912	1.14	1.10–1.17	0.001
Total (random effects)	788/944	867/912	1.13	1.10–1.17	0.001
Pooled proportion (%)	83.5	95.1			

[1] I^2 = proportion of total variation of effect size estimates that is due to heterogeneity.
[2] Relative risk for having a blood progesterone concentration below a certain threshold at the end of the Ovsynch protocol using a single $PGF_{2\alpha}$ treatment (1PGF) compared with 2 $PGF_{2\alpha}$ treatments (2PGF) during the Ovsynch protocol.

Meta-analysis: 2X vs 1X PGF increased CL reg. ~12 p.p.

Sequential PGF treatm. (two/24 h) increased P/AI

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Short communication: Effect of adding a second prostaglandin $F_{2\alpha}$ injection during the Ovsynch protocol on luteal regression and fertility in lactating dairy cows: A meta-analysis

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†Department of Dairy Science, University of Wisconsin, Madison 53706

Table 3. Effect of an additional treatment with $PGF_{2\alpha}$ during the Ovsynch protocol (n = 5,356) on pregnancy per AI considering 6 manuscripts with a randomized controlled study design

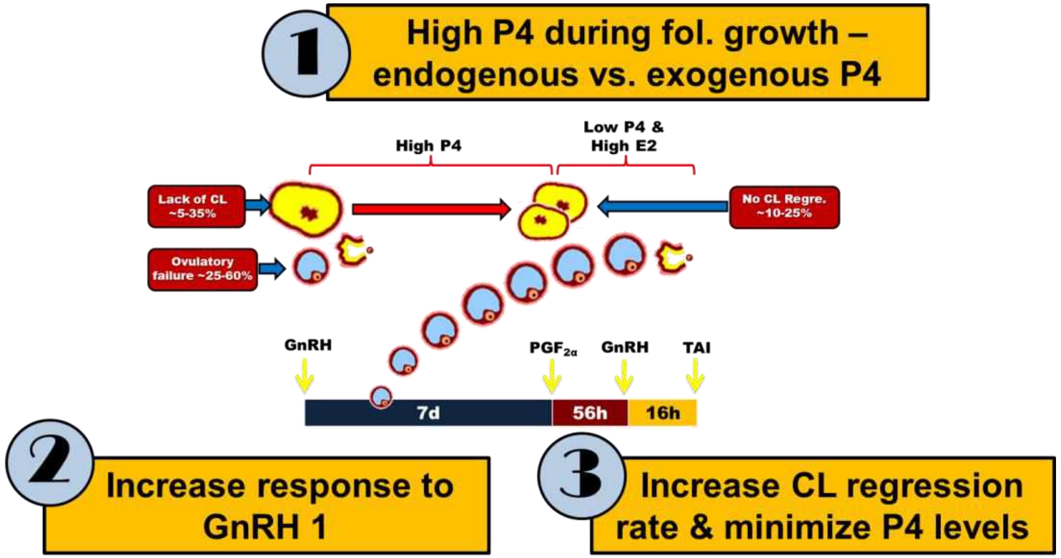
Manuscript[1]	Pregnancy per AI		Relative risk[2]	95% CI	P-value
	1PGF	2PGF			
Barletta et al. (2018)	107/349	137/387	1.15	0.94–1.42	
Brusveen et al. (2009)	78/197	88/182	1.22	0.9	
Carvalho et al. (2015a)	150/462	168/435	1.19	1.0	
Heidari et al. (2017)	49/149	54/144	1.14	0.8	
Santos et al. (2016)	95/266	111/268	1.16	0.9	
Wiltbank et al. (2015)	436/1,266	471/1,251	1.09	0.9	
I^2 = 0.00% (P = 0.942)					
Total (fixed effects)	915/2,689	1,029/2,667	1.14	1.0	
Total (random effects)	915/2,689	1,029/2,667	1.14	1.0	
Pooled proportion (%)	34.0	38.6			

[1] I^2 = proportion of total variation of effect size estimates that is due to heterogeneity.
[2] Relative risk for conceiving at timed AI using a single $PGF_{2\alpha}$ treatment (1PGF) compared with 2 $PGF_{2\alpha}$ treatments (2PGF) during the Ovsynch protocol.

Meta-analysis: 2X vs 1X PGF increased P/AI ~4.6 p.p.

Summary for strategies for optimizing TAI programs for dairy cows

- **Endocrine status** and **stage of ovarian structure development** at the time of key hormonal treatments **affects the response** to individual treatments and thus, whole protocol



- **Equivocal evidence** to support **increasing dose of GnRH** at beginning of breeding-Ovsynch to improve P/AI – effects might analog or salt dependent

- **Supportive evidence** for giving **two doses of PGF 24 h apart** and **growing evidence** that a **double PGF** dose before TAI might improve P/AI – effects might be **parity specific**

Acknowledgement

Cornell University
College of Agriculture and Life Sciences

Dairy Cattle Biology & Management Laboratory

United States Department of Agriculture
National Institute of Food and Agriculture

NY farm viability INSTITUTE

This work was supported by the **USDA National Institute of Food and Agriculture**, Animal Health Program **Project # 2017-67015-26772, Hatch project NYC-2020-21-255**, and **Multistate project 1021189**. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the National Institute of Food and Agriculture (NIFA) or the United States Department of Agriculture(USDA)".

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Thank You! Questions?