NDSU NORTH DAKOTA STATE UNIVERSITY

STUDENT FOCUSED • LAND GRANT • RESEARCH UNIVERSITY

Embryonic and Foetal Programming

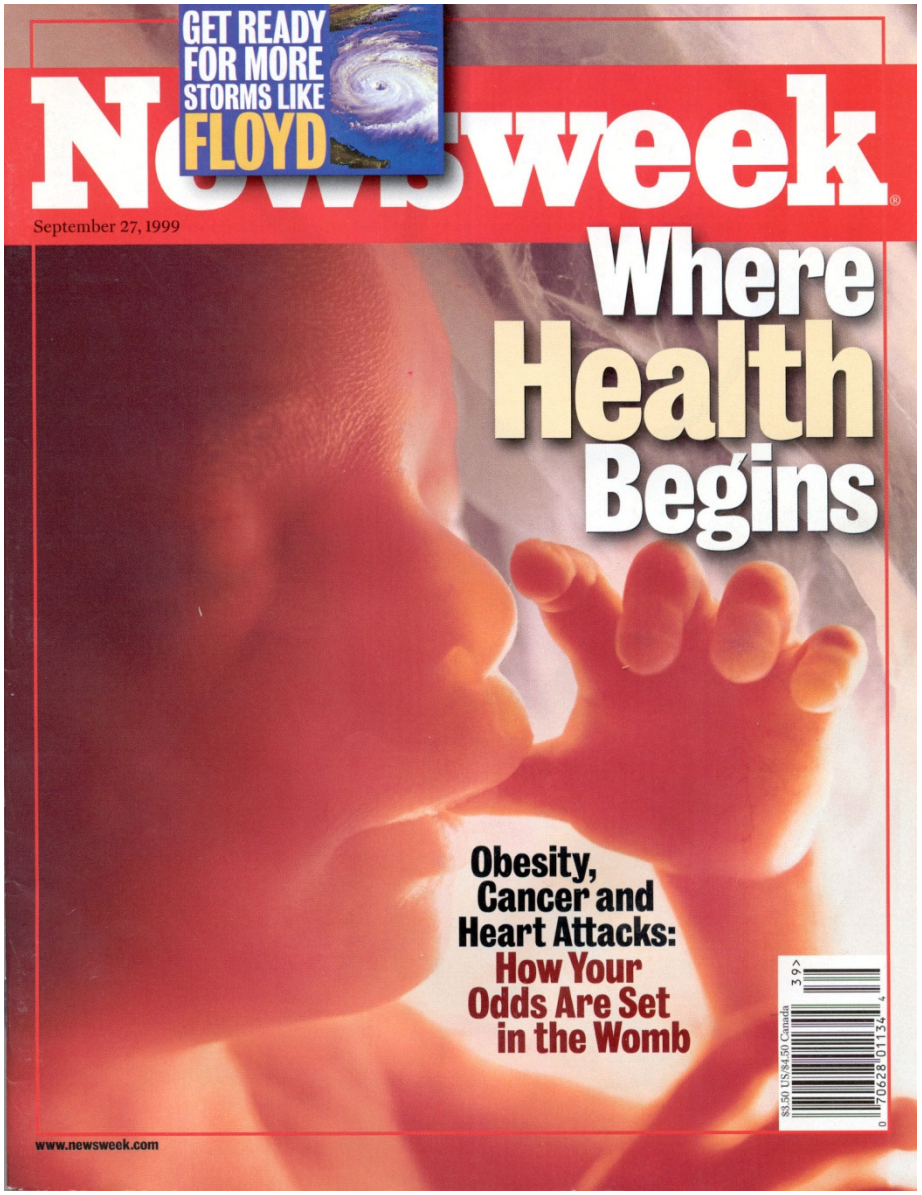
Session 21.

ASAS Session

Programming

- The process through which a ***stimulus*** or ***insult*** establishes a ***permanent*** response

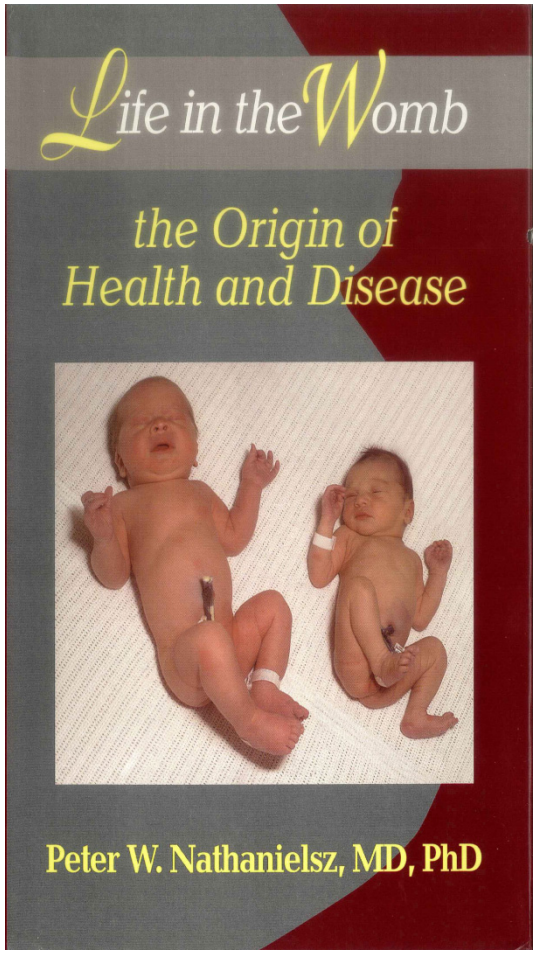
- **Developmental programming hypothesis**
- Exposure during a ***critical period*** in development may influence later metabolic or physiological functions in adult life

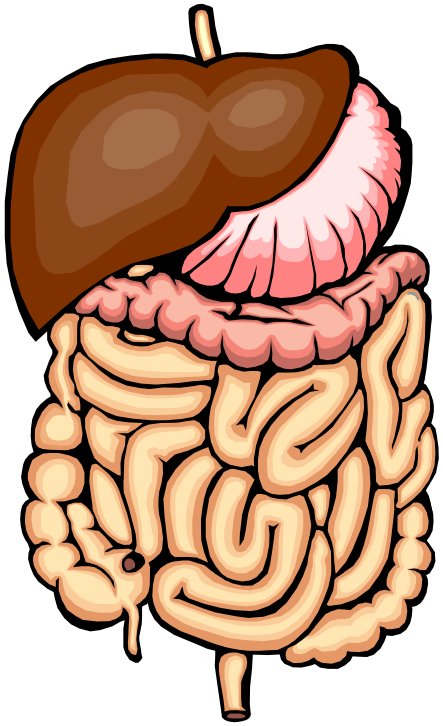

GET READY FOR MORE STORMS LIKE FLOYD
Newsweek
September 27, 1999
Where Health Begins
Obesity, Cancer and Heart Attacks: How Your Odds Are Set in the Womb
$3.50 US/$4.50 Canada
www.newsweek.com


OCTOBER 4, 2010
Environment Special:
The oceans—why 70% of our planet is in danger
The Facebook Movie:
The secret history of social networking
TIME
How the first nine months shape the rest of your life
The new science of fetal origins
BY ANNIE MURPHY PAUL

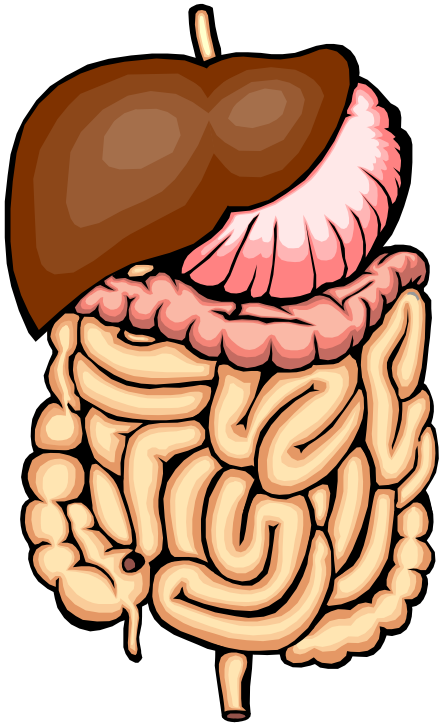
10 PRINCIPLES OF DEVELOPMENTAL PROGRAMMING

6) **Compensation carries a price.** In an unfavorable environment, the developing baby makes attempts to compensate for deficiencies. However, the compensatory effort often carries a price.





?



?


©Silverander, EthnoGraphies®

Livestock consequences?

- Placental adaptations to maternal nutrition
  - Kimberly Vonnahme
- The Copenhagen Sheep Model
  - Mette Nielsen
- Consequences in beef cattle production
  - Paul Greenwood
- Consequences in sheep production
  - Sue McCoard

Assessing placental function in our livestock species to ensure adequate fetal development

Kimberly Vonnahme, PhD
Associate Professor
Department of Animal Sciences

Acknowledgements

- Collaborators at NDSU
  - Kendall Swanson
  - Joel Caton
  - Christopher Schauer
  - Steve O'Rourke
  - Larry Reynolds
  - Dale Redmer
  - Anna Grazul-Bilska
  - Justin Luther
  - Carrie Hammer
  - Greg Lardy
  - Kasey Carlin
  - Eric Berg
- Other collaborators
  - Rick Funston—UNL
  - Bret Taylor—USDA-ARS SES
  - Caleb Lemley– MSU
- Students and Staff
  - Bethany Mordhorst
  - Arshi Reyaz
  - Leslie Lekatz
  - Leticia Camacho
  - Victoria Kennedy
  - Allison Meyer
  - Tammi Neville
  - Jim Kirsch
  - Jake Reed

NDSU Animal Nutrition and Physiology Center

OUTLINE

- Background
  - Maternal blood volume
  - Need for placental adaption to change

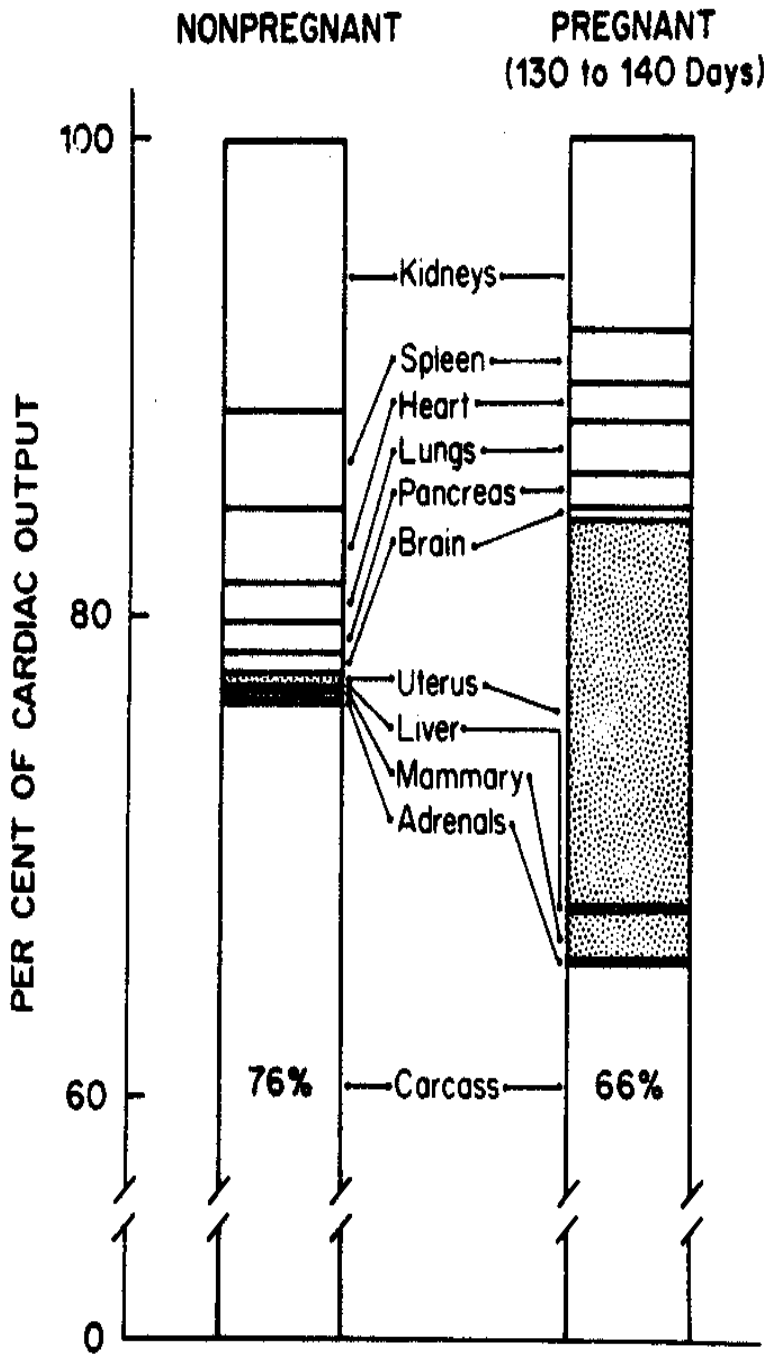
- Focus on blood flow in current models
  - Nutrition in sheep and beef cattle
    - Nutrient restriction
      - Melatonin
      - Timing of realimentation
    - Protein

Blood distribution during pregnancy

- Uteroplacental blood flow increases dramatically to support the nutritional demands of the rapidly growing fetus
- Increased maternal plasma volume
  - 30 to 40% increase
- Increased maternal cardiac output
  - 35% increase in stroke volume
  - 15% increase in heart rate
- Fractional distribution of cardiac output to the uterus

- % of Cardiac Output
  - 0.5% non-pregnant
  - >16% late pregnant
- Note: the % of cardiac output delivered to the other tissues falls, however, absolute values of blood flow are unchanged, further pointing to the need for an expanded blood volume

Rosenfeld, 1984

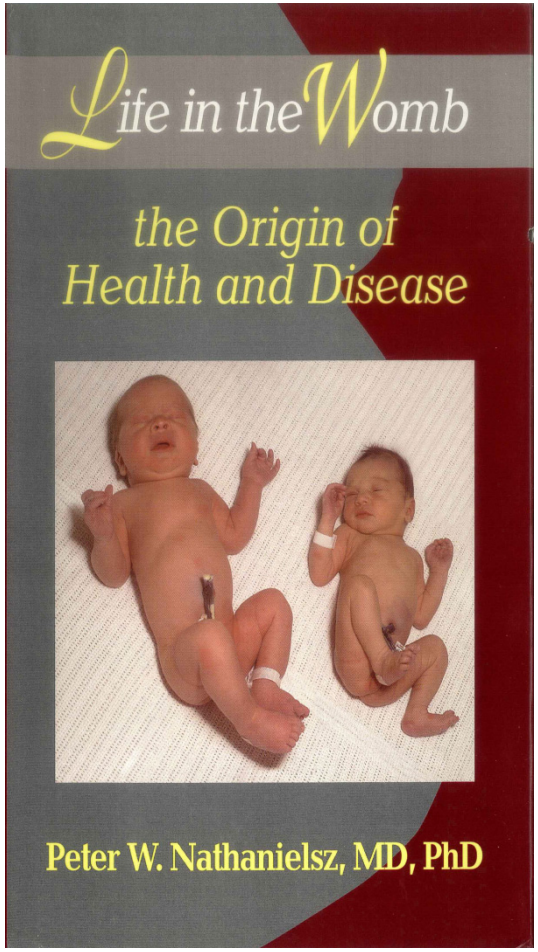


Nourishing the uteroplacenta

- Uterine/ umbilical blood flows are increased during pregnancy
  - –Vascular remodeling
  - –Vasodilatation

10 PRINCIPLES OF DEVELOPMENTAL PROGRAMMING

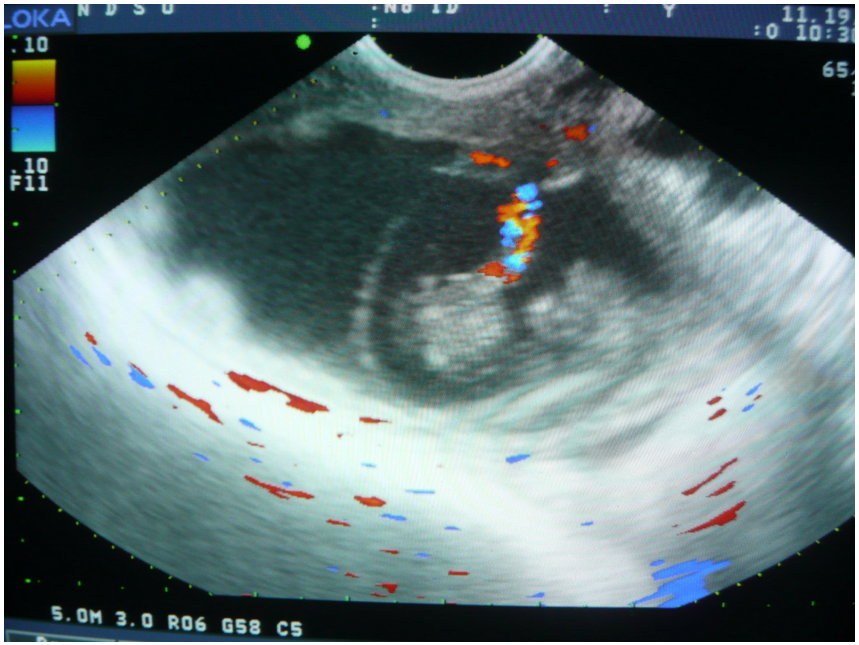
5) The placenta plays a key role in programming.



SHEEP AND COW PLACENTAS

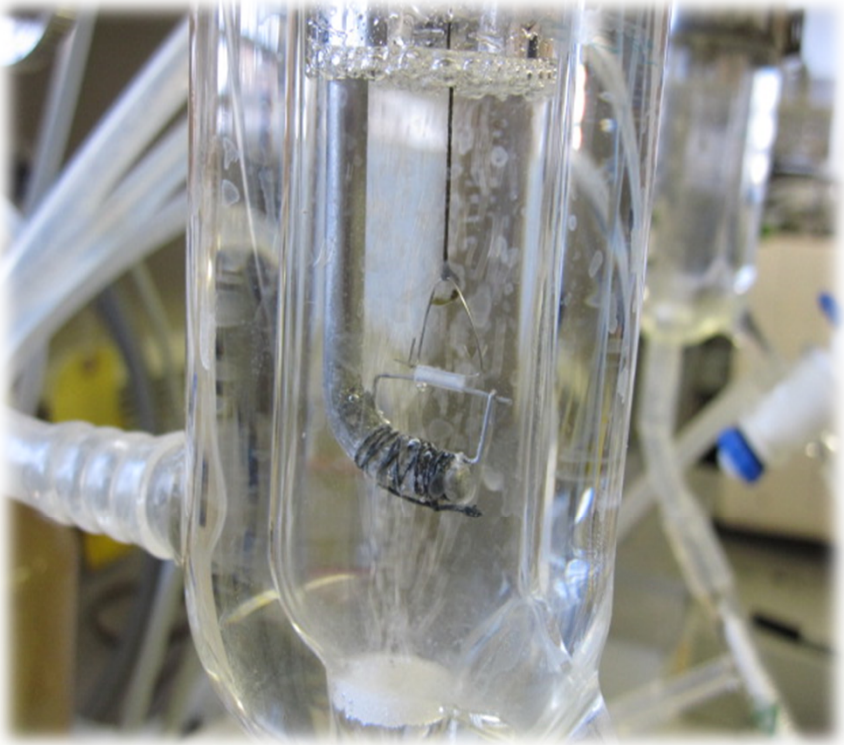
Goal of my lab

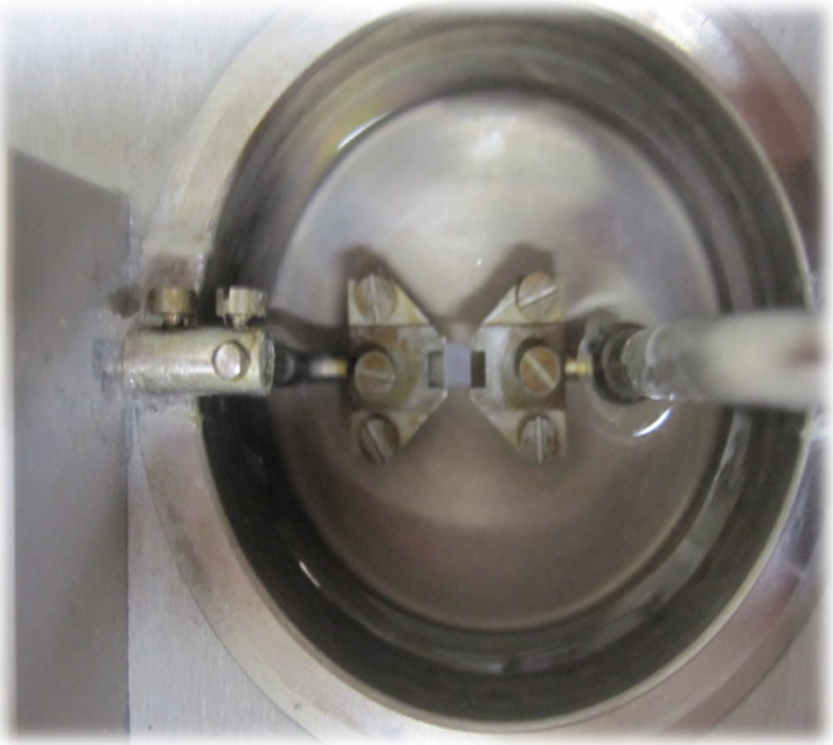
- How is nutrition altering placental function?

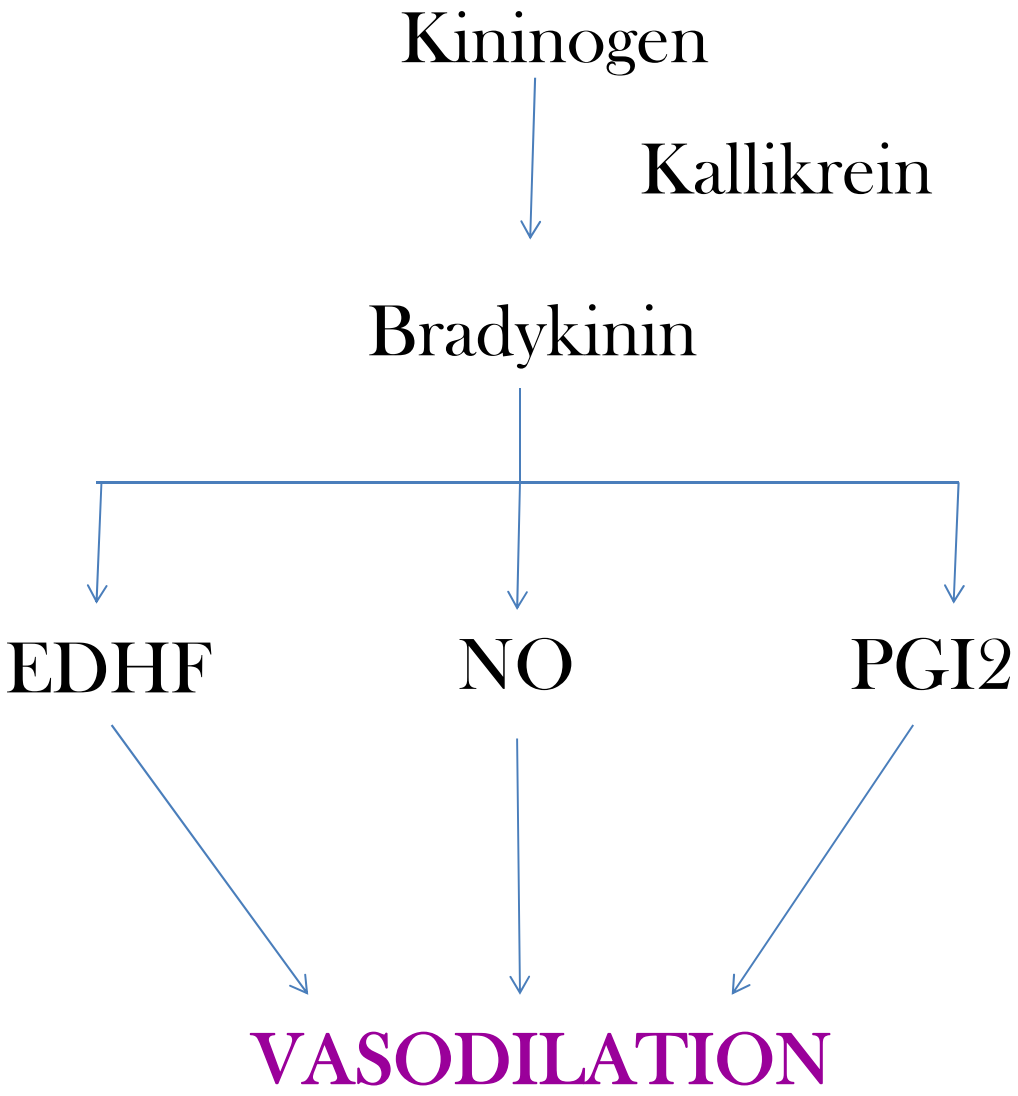


Goal of my lab

- How is nutrition altering placental function?

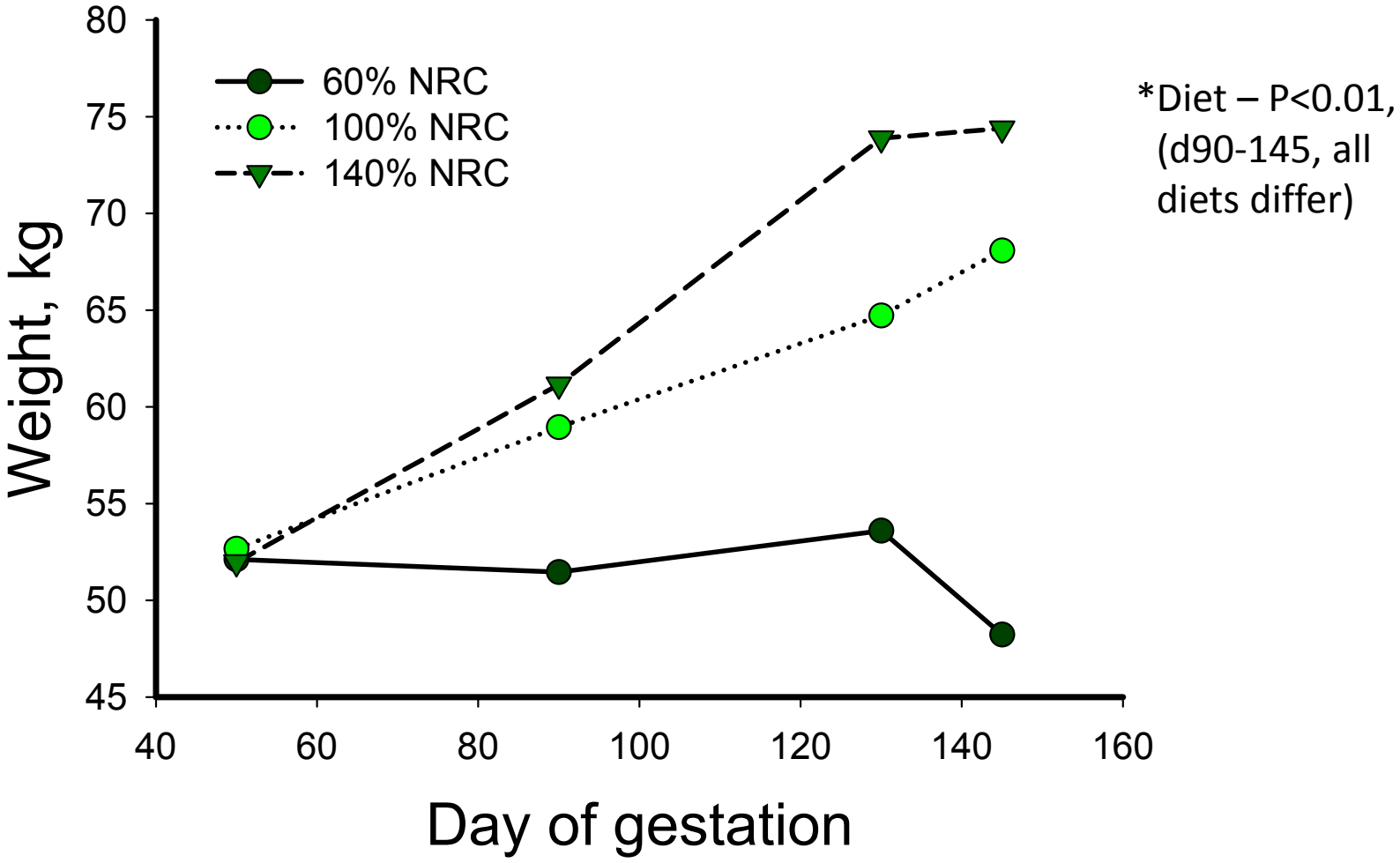




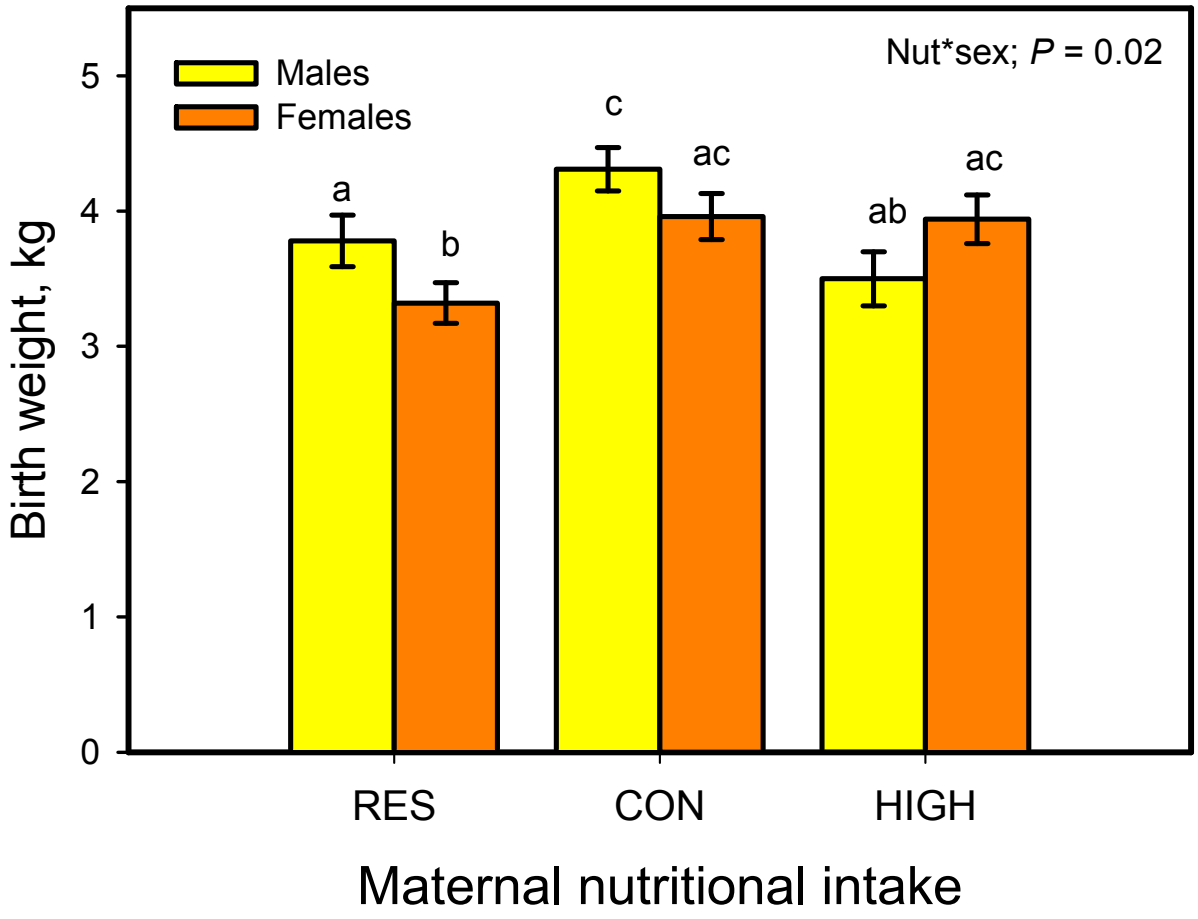

Kininogen
Kallikrein
Bradykinin
EDHF
NO
PGI2
VASODILATION

Global Nutrition

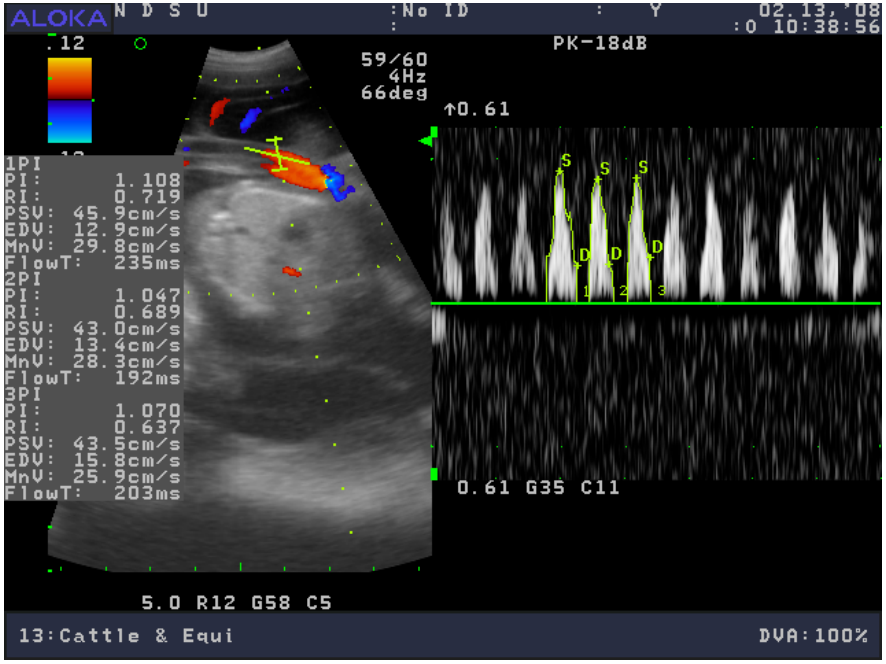
Maternal intake and BW changes

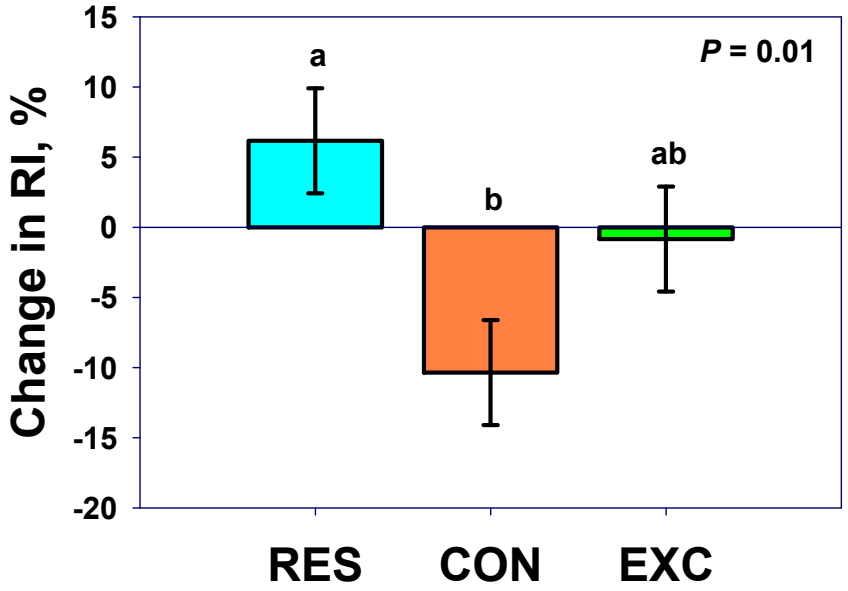


*Diet – P<0.01, (d90-145, all diets differ)


Nut*sex; P = 0.02
Males
Females
Birth weight, kg
0
1
2
3
4
5
a
b
c
ac
ab
ac
RES
CON
HIGH
Maternal nutritional intake

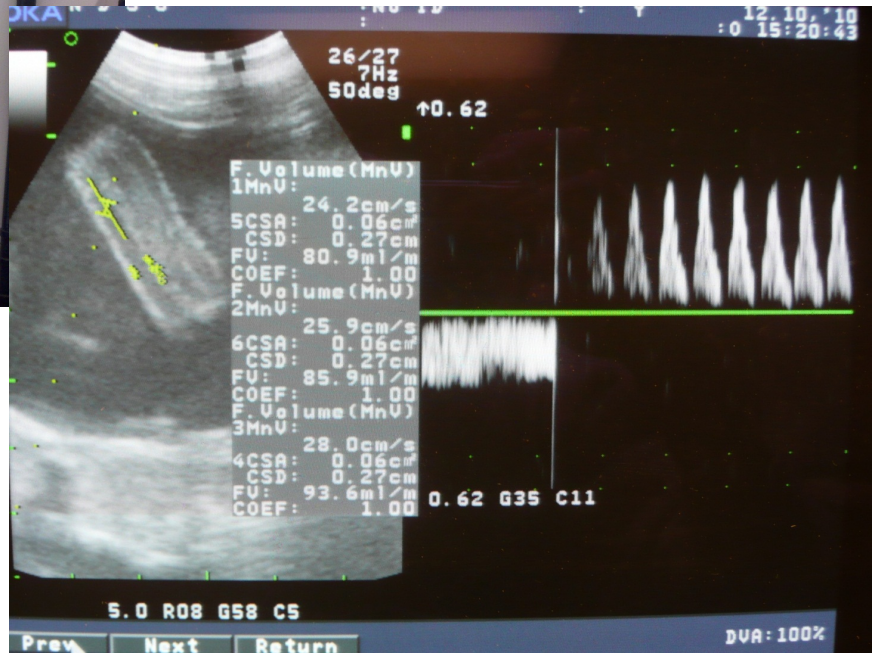
Umbilical Hemodynamics in Pregnant Ewes



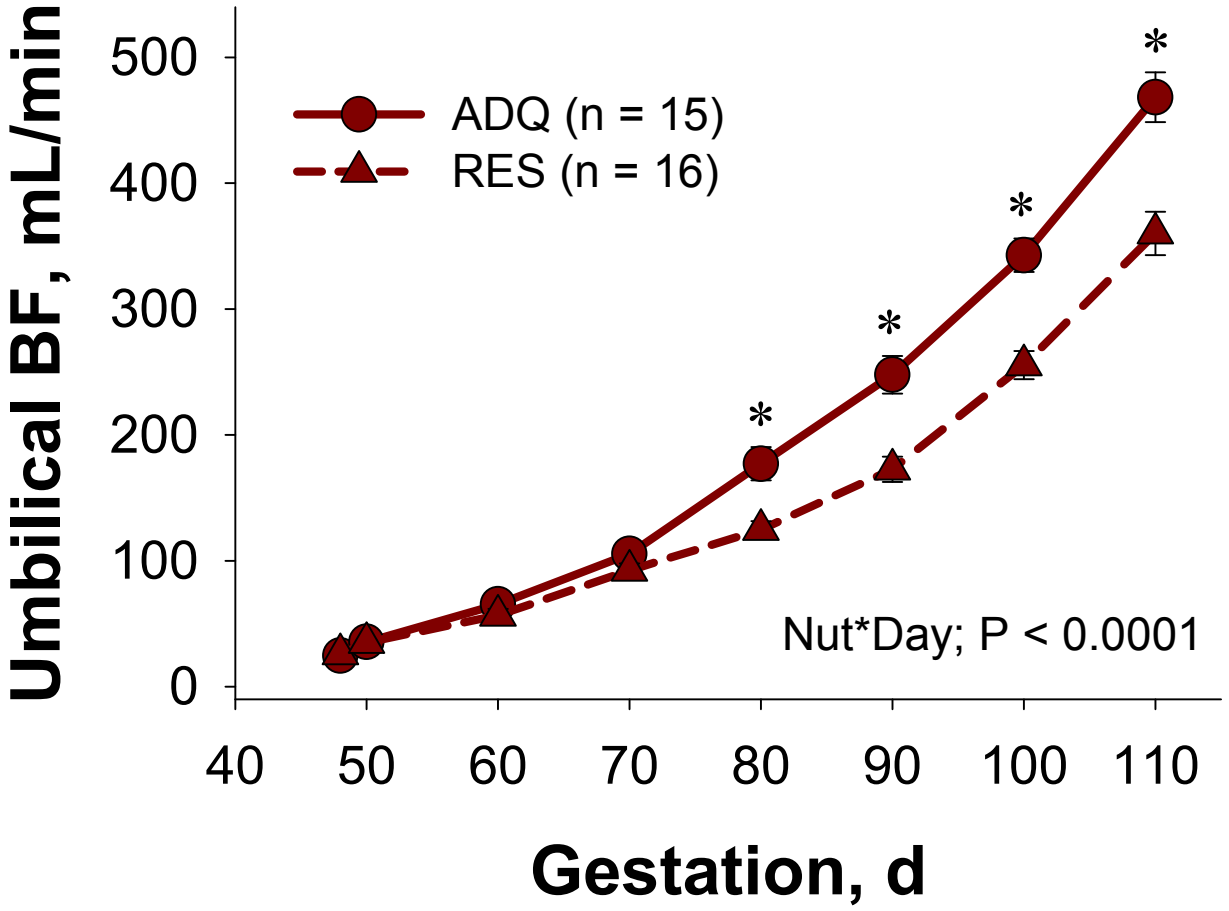


Lekatz et al., 2009

Can Melatonin Help?

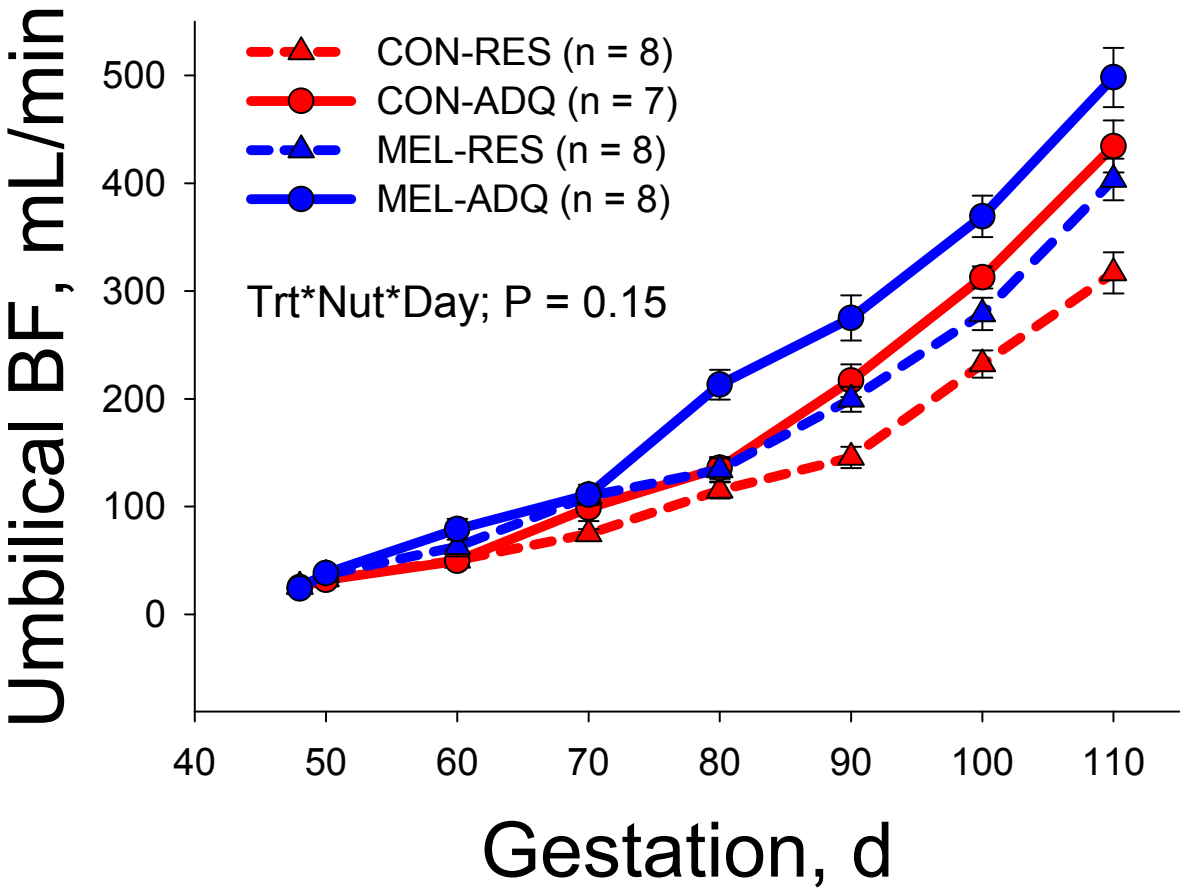


Umbilical Blood Flow



Lemley et al., 2012

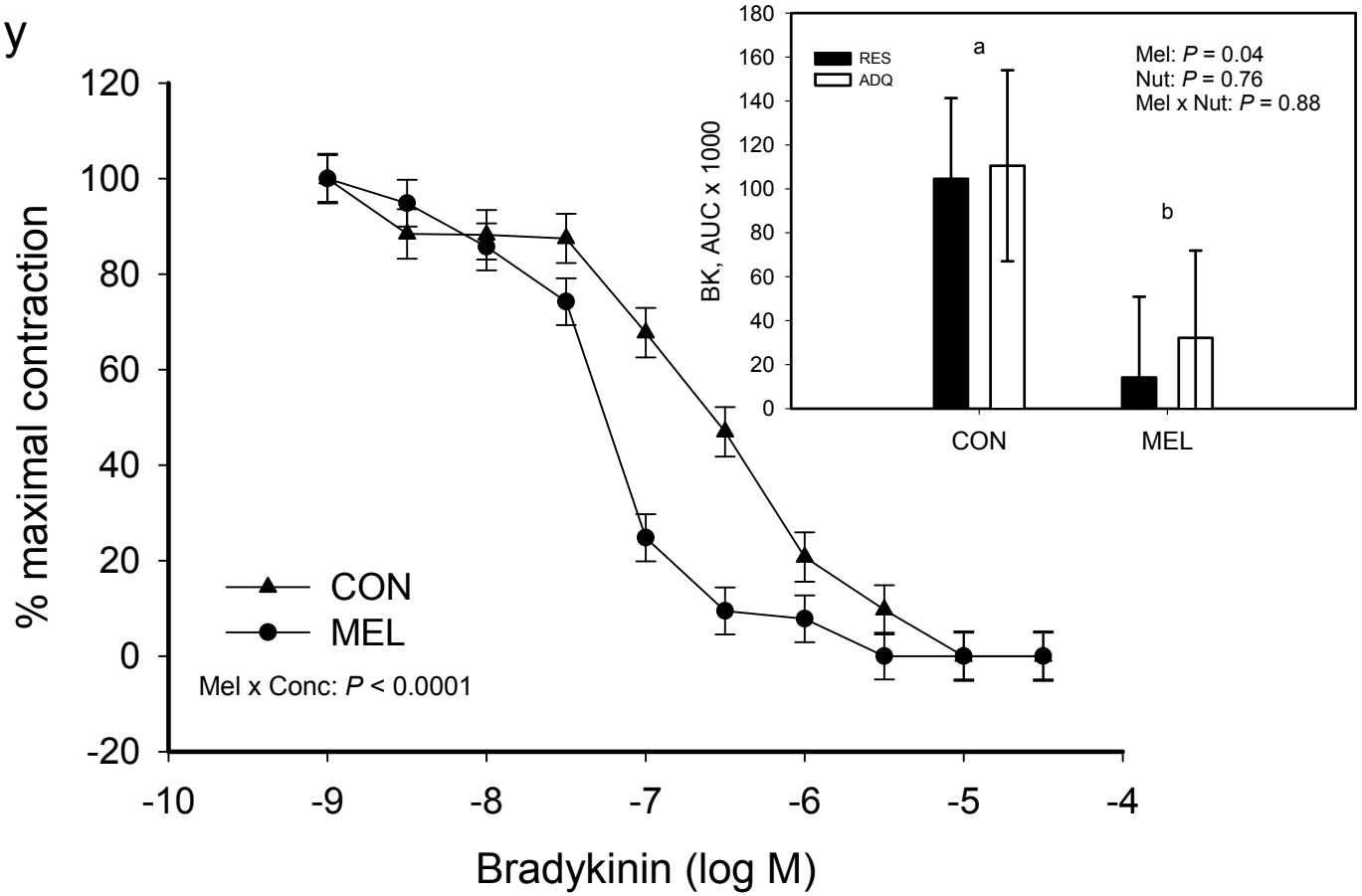
Umbilical Blood Flow



Lemley et al. (2012) AJP.

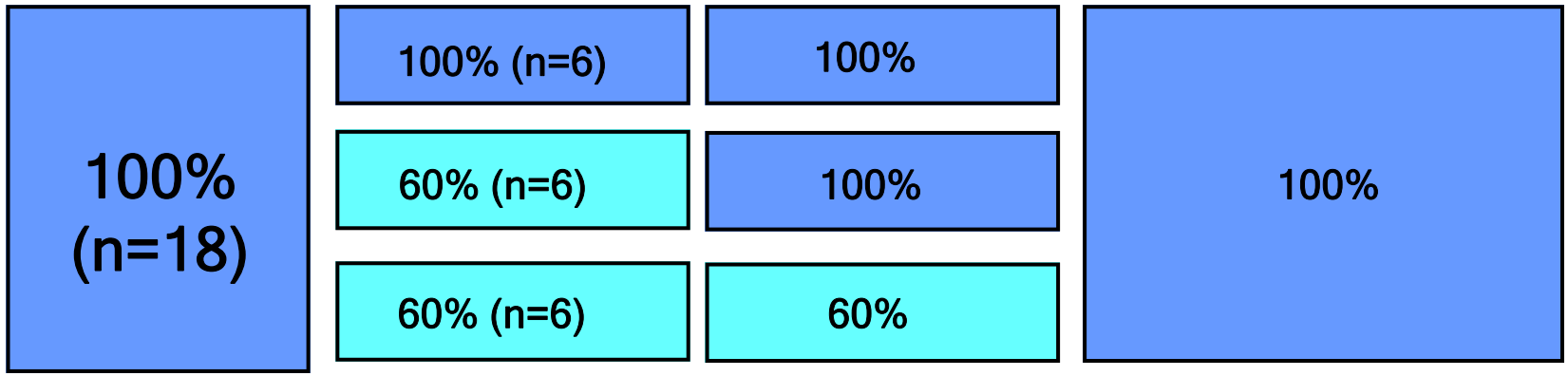
Melatonin enhances vasodilation

*Cot only



What about early blood flow?

Percentage NRC recommendations

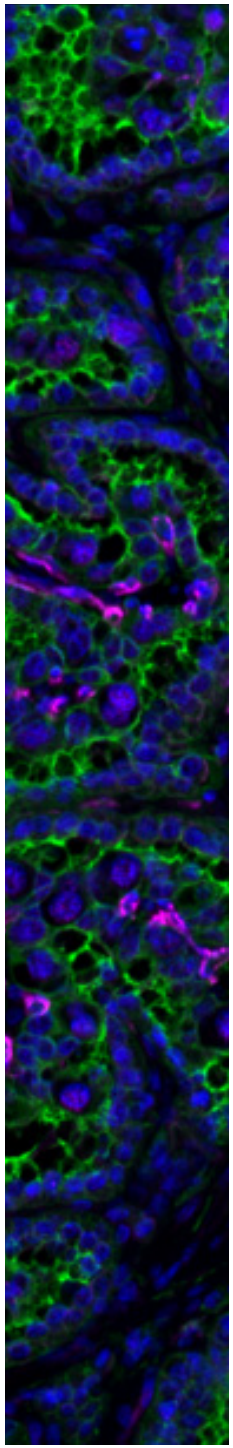


Things that make you go Hmmmmm….

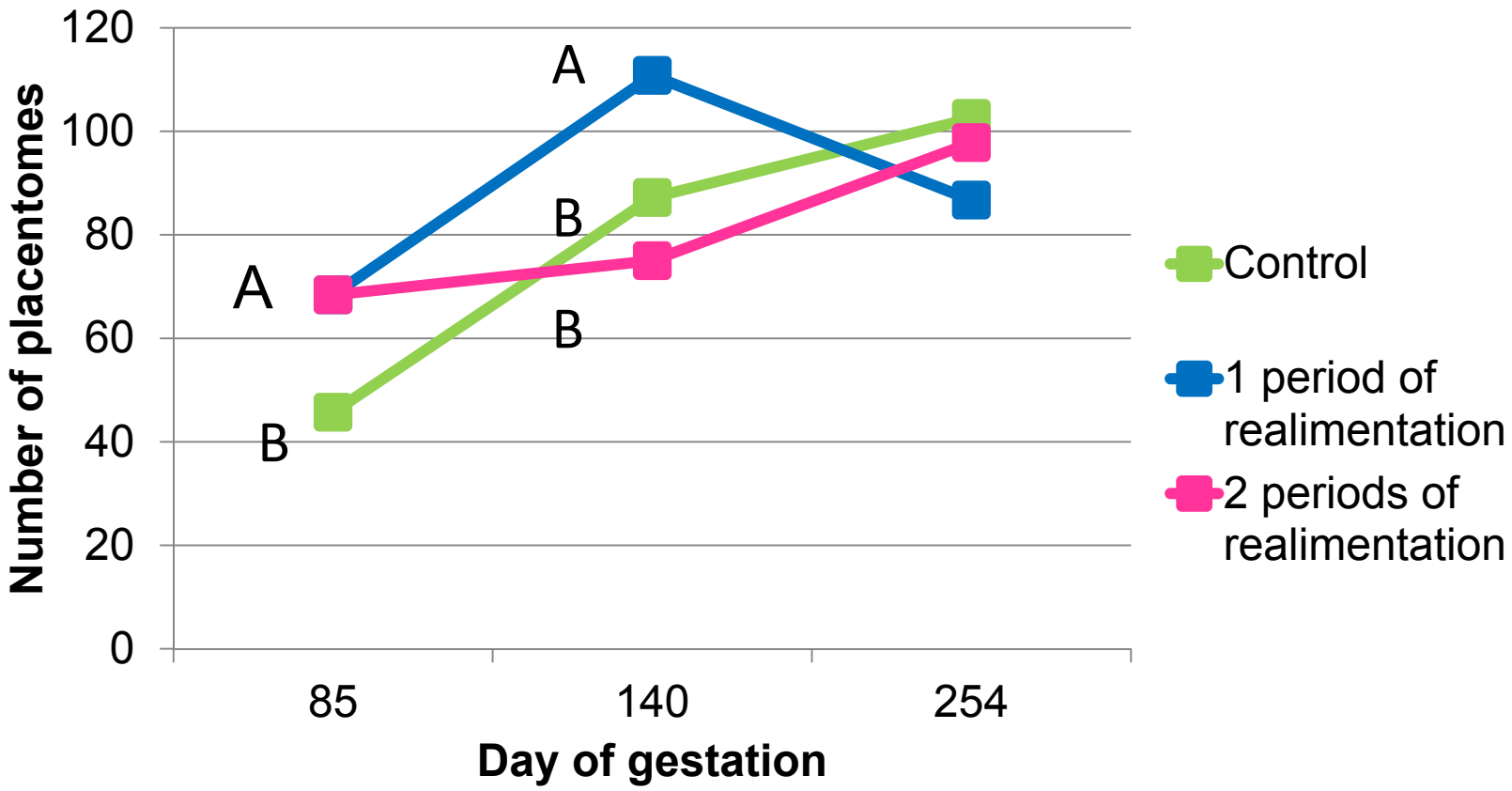
Day 85	Control	Restricted	SEM	P-value
Fetal wt, g	**116.9**	**138.9**	**8.0**	**0.07**
CRL, cm	17.0	17.0	0.01	0.28
Girth, cm	**10.3**	**10.8**	**0.16**	**0.04**
Placental wt, g	**84.8**	**118.7**	**5.9**	**0.002**

Fetal wt, kg	CC/CCC	RC/RRC	RR/RRC	SEM	P-value
140	2.03	2.14	2.16	0.12	0.54
254	30.33	29.80	31.00	2.40	0.84

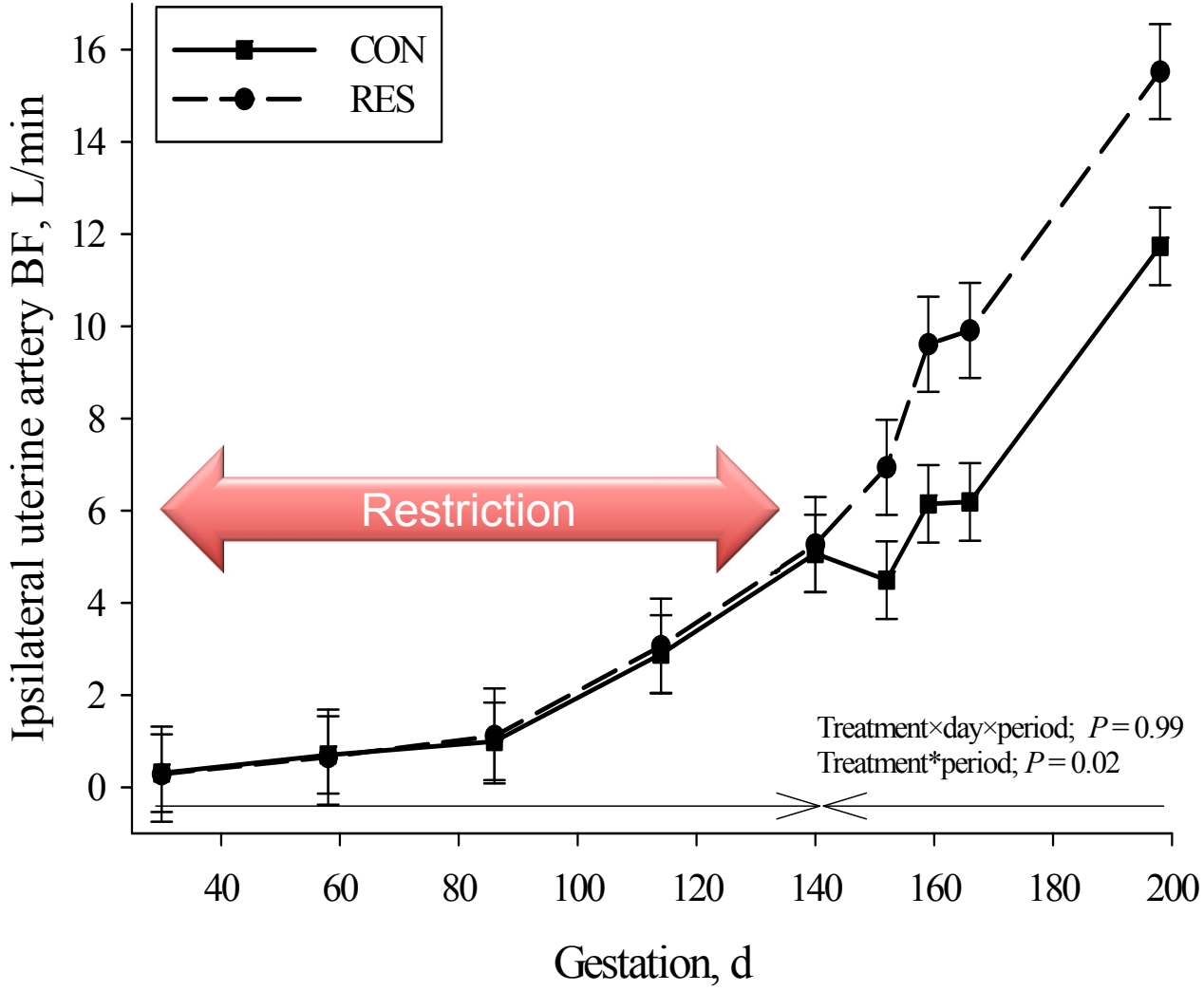
Camacho et al., unpublished



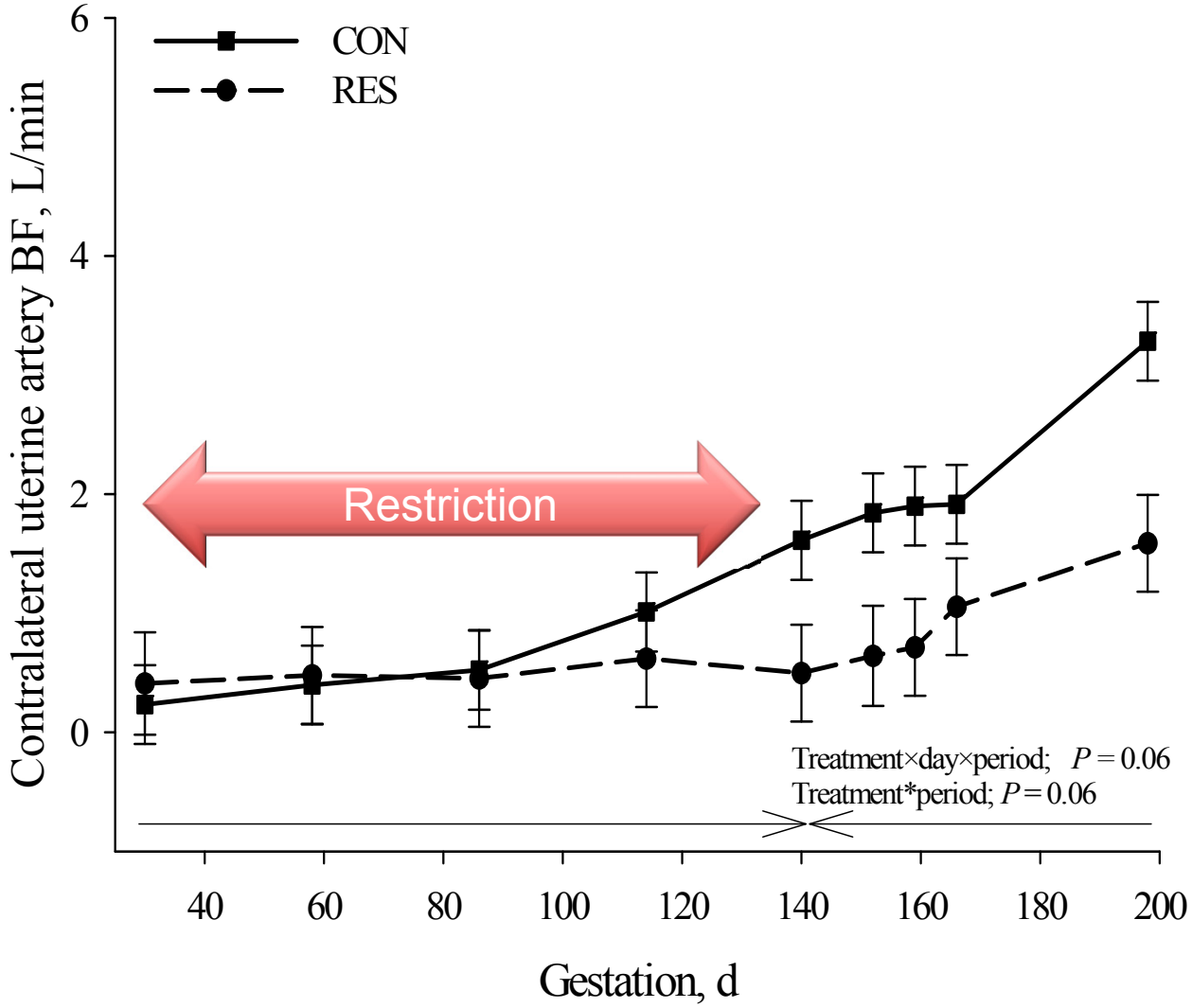
Study by Camacho et al.



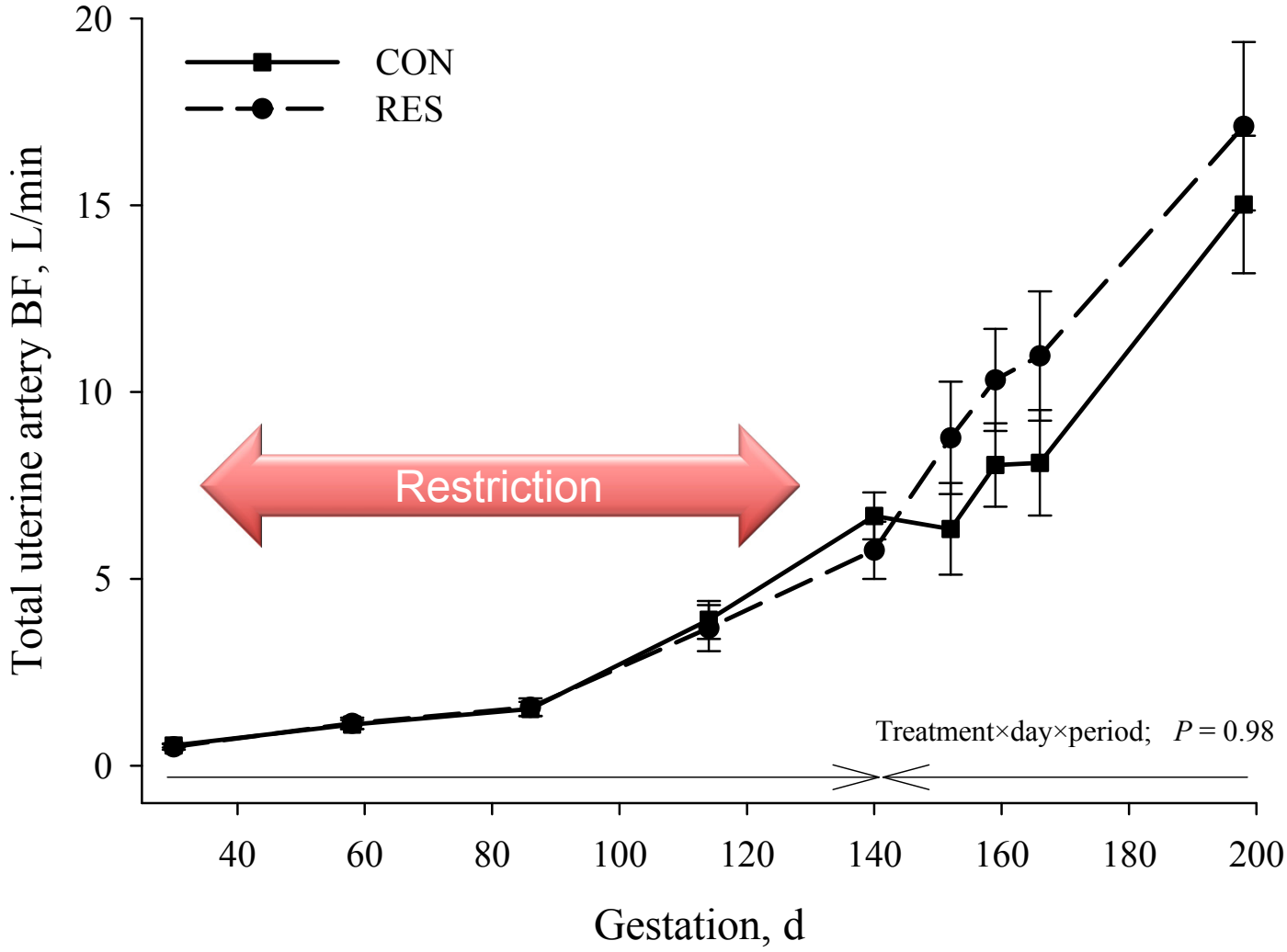
Camacho et al., 2014



Camacho et al., 2014

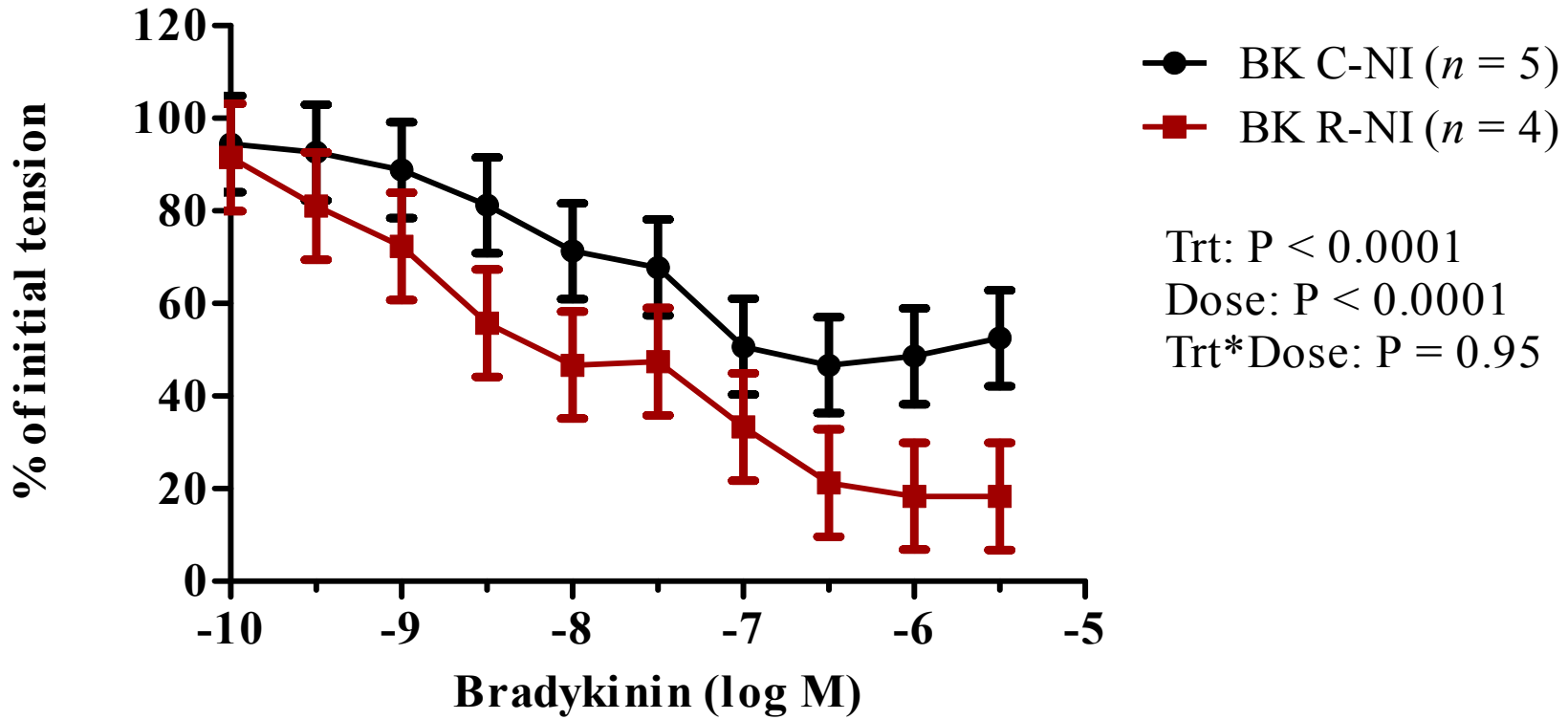


Camacho et al., 2014



Reyaz et al., unpublished

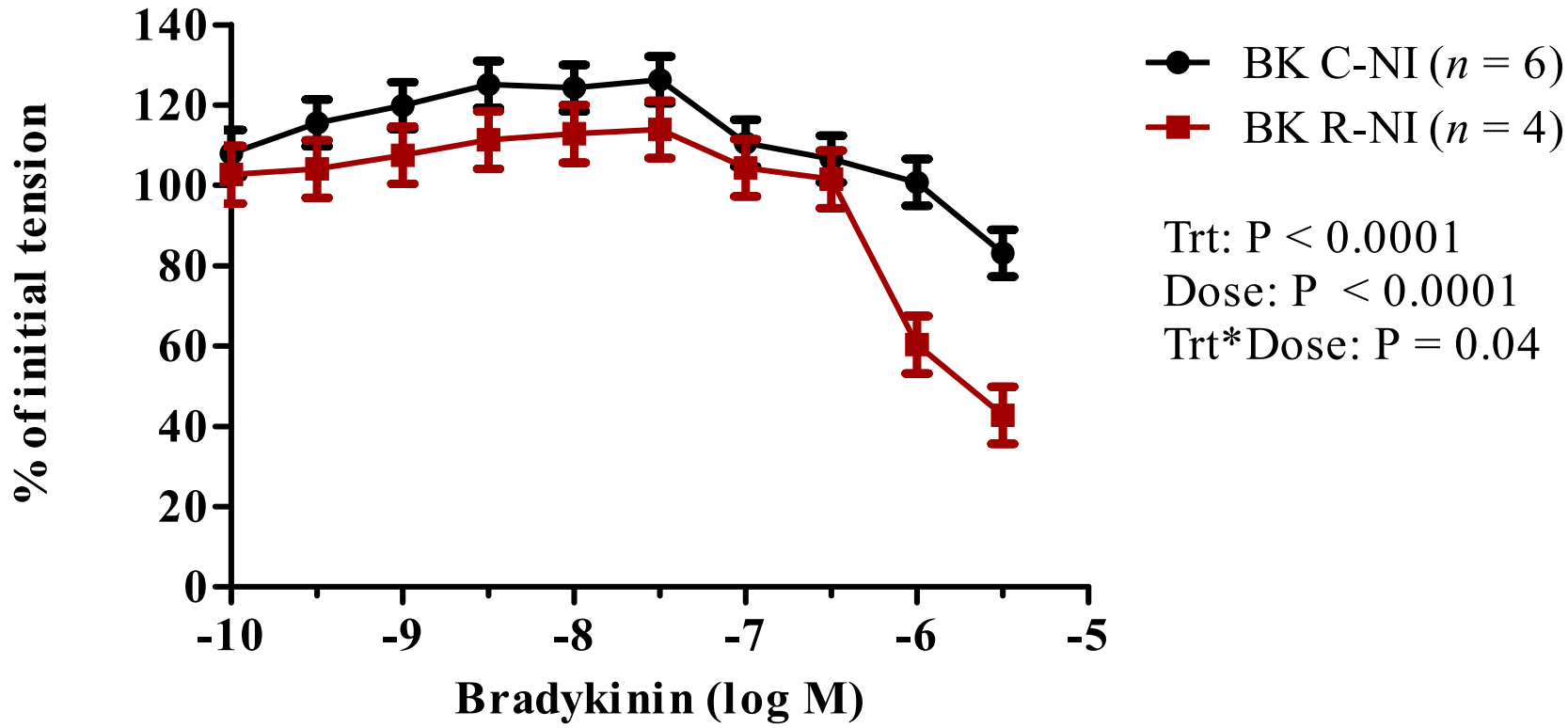
CAR (BK) - D 85



Relaxation responses to BK were recorded after pre-contracting CAR arteries with 1μM NE and COT arteries with 1μM U46619.

COT (BK) - D 85

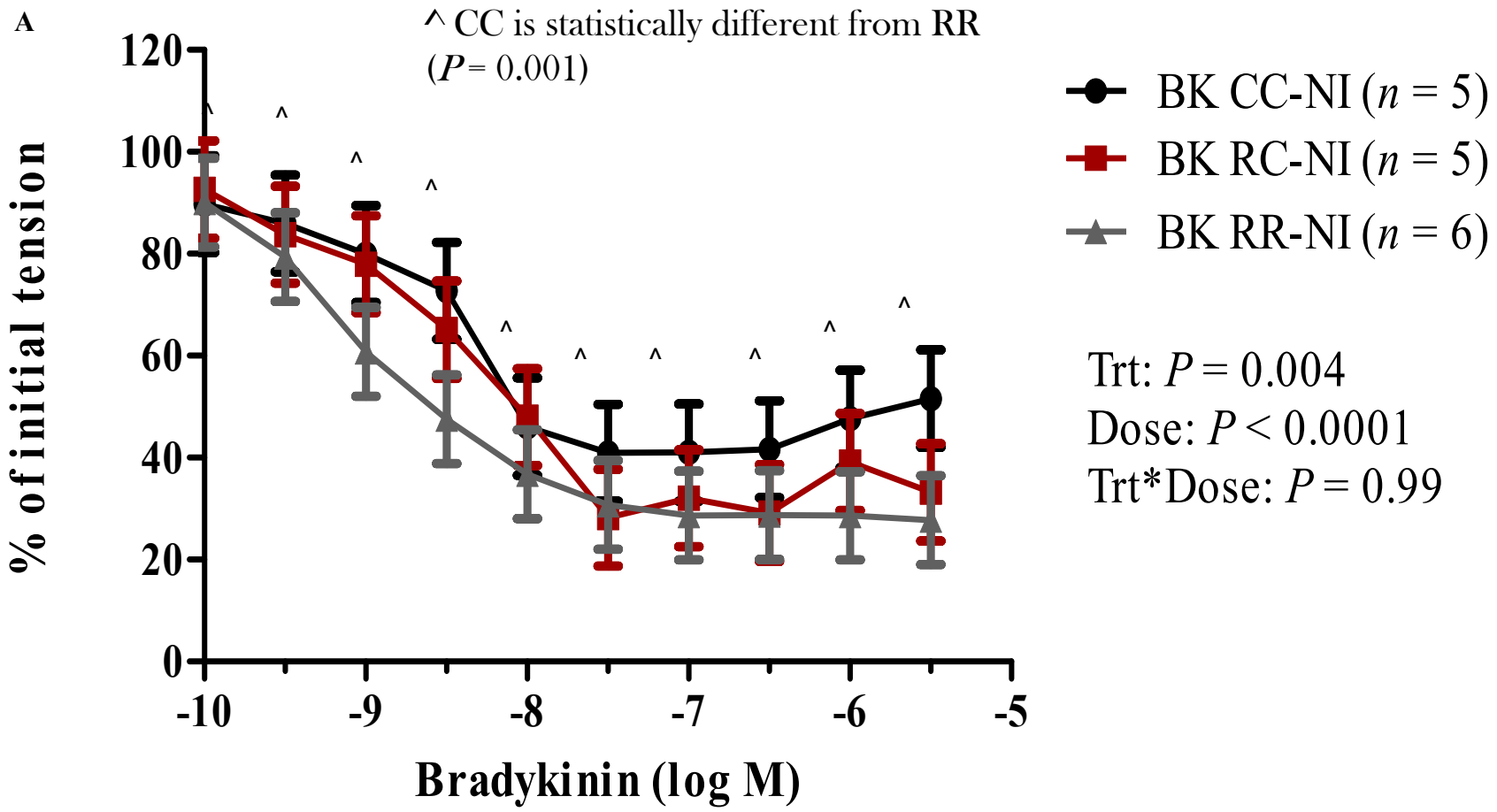
Reyaz et al., unpublished



Relaxation responses to BK were recorded after pre-contracting CAR arteries with 1μM NE and COT arteries with 1μM U46619.

CAR (BK) – D 140

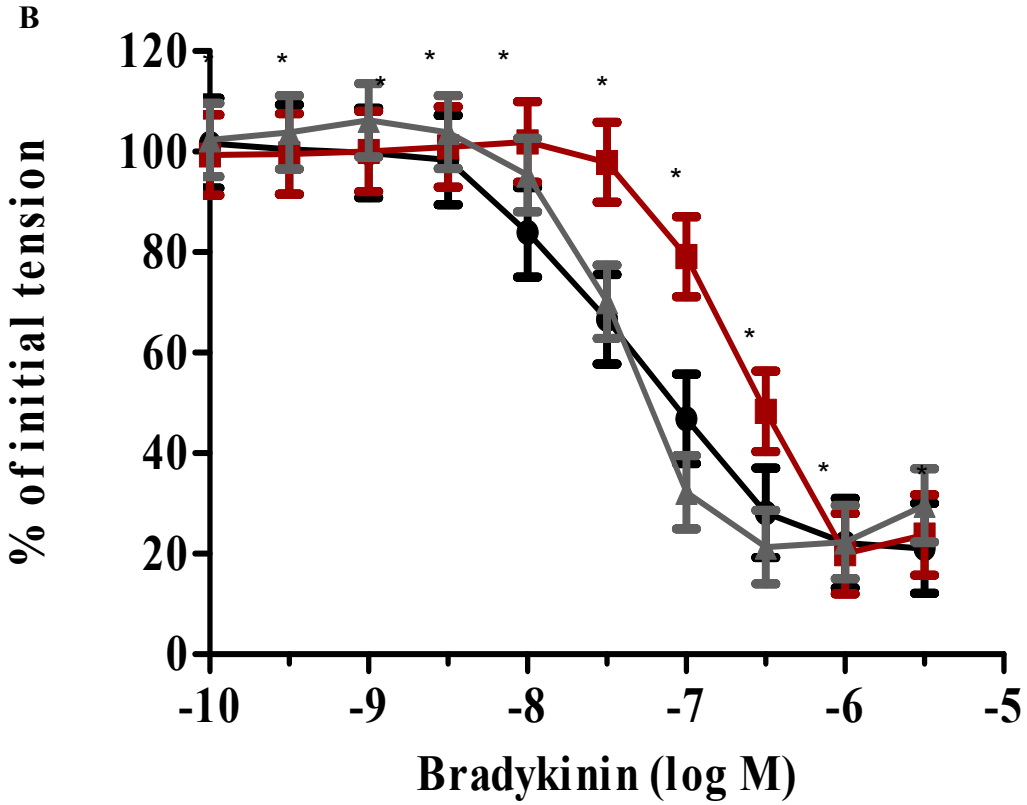
Reyaz et al., unpublished



Relaxation responses to BK were recorded after pre-contracting CAR arteries with 1μM NE and COT arteries with 1μM U46619.

COT (BK) – D 140

Reyaz et al., unpublished



*RC is statistically different from CC ($P = 0.008$)
*RC is statistically different from RR ($P < 0.02$)

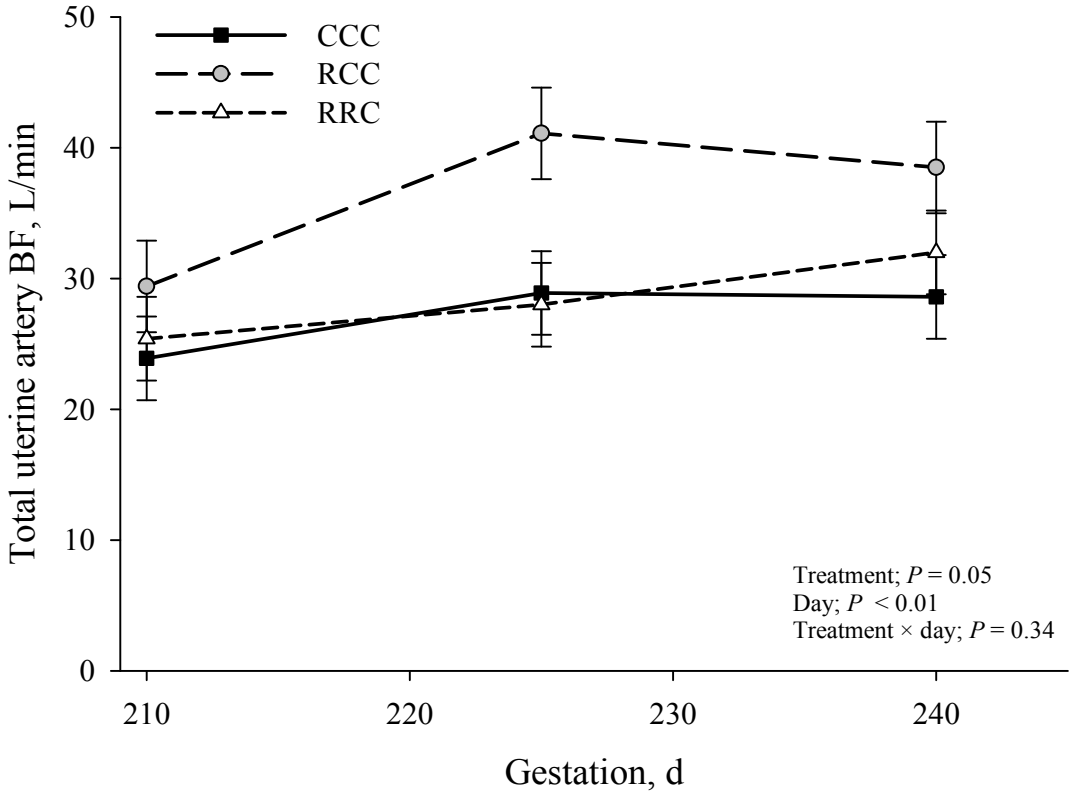
BK CC-NI ($n = 4$)
BK RC-NI ($n = 5$)
BK RR-NI ($n = 6$)

Trt: $P = 0.01$
Dose: $P < 0.0001$
Trt*Dose: $P = 0.06$

Relaxation responses to BK were recorded after pre-contracting CAR arteries with 1μM NE and COT arteries with 1μM U46619.

Camacho et al., unpublished

Uterine blood flow



Summary of Nutrient Restriction

- Cattle and sheep differ in their response to nutrient restriction
  - Caution: timing of NR & age of dam differed
- Placental vascular function differences
  - In the ewe, primarily COT
  - In the cow, both
- What is the response of the ewe upon realimentation?

Sheep MP project

- Assigned to 1 of 3 treatments (n = 6/trt)
- Individually fed LOW, CON, HIGH from d 100 to 130

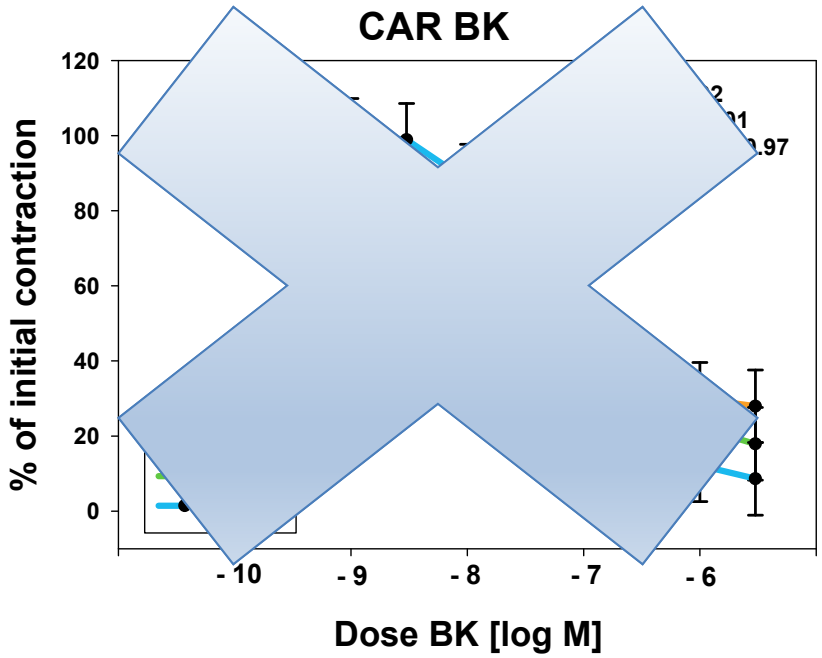
LOW
Fed 60% MP

CON
Fed 100% MP requirements

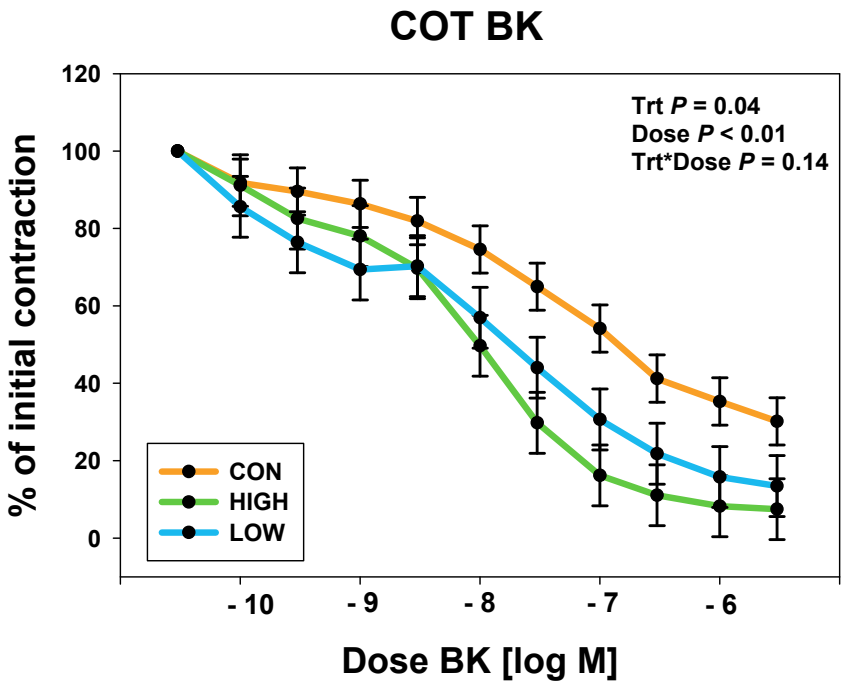
HIGH
Fed 140% MP

Results: BK

Maternal

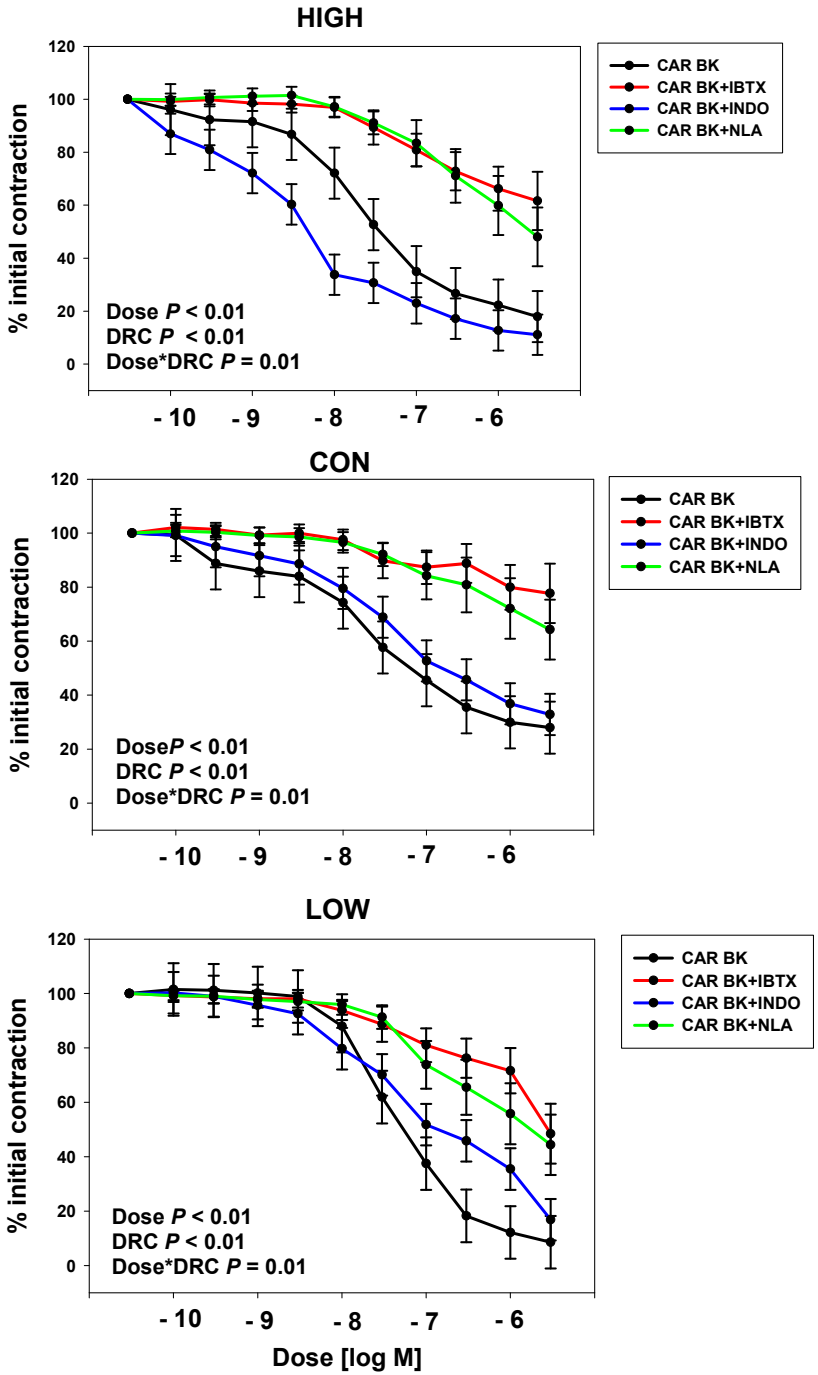


Fetal



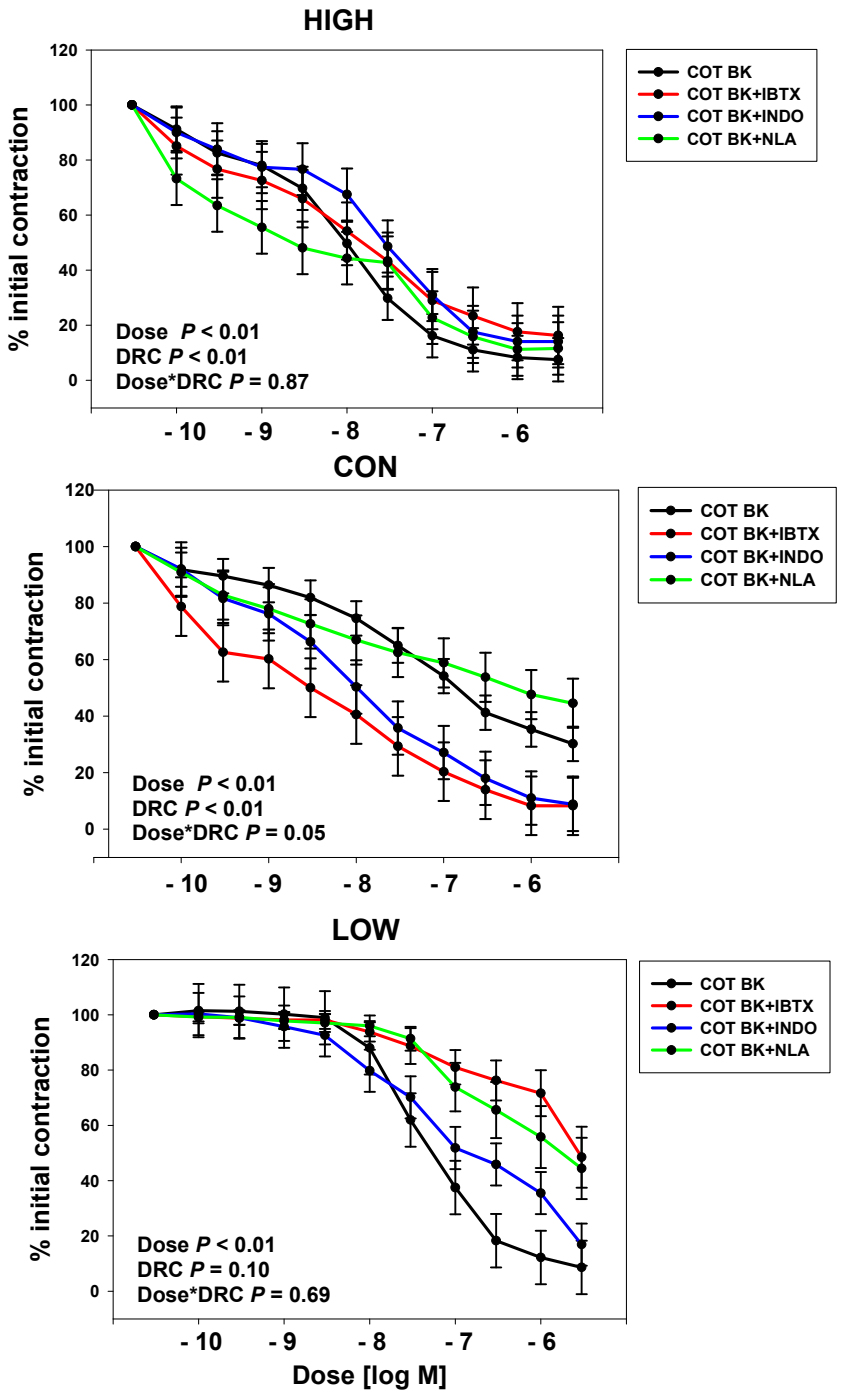
Results: CAR DRCs

- Inhibiting PGI2 still results in vasorelaxation
  - Mechanism does not involve PGI2
- Inhibiting EDHF and NO delays vasorelaxation
  - Mechanism involves EDHF and NO

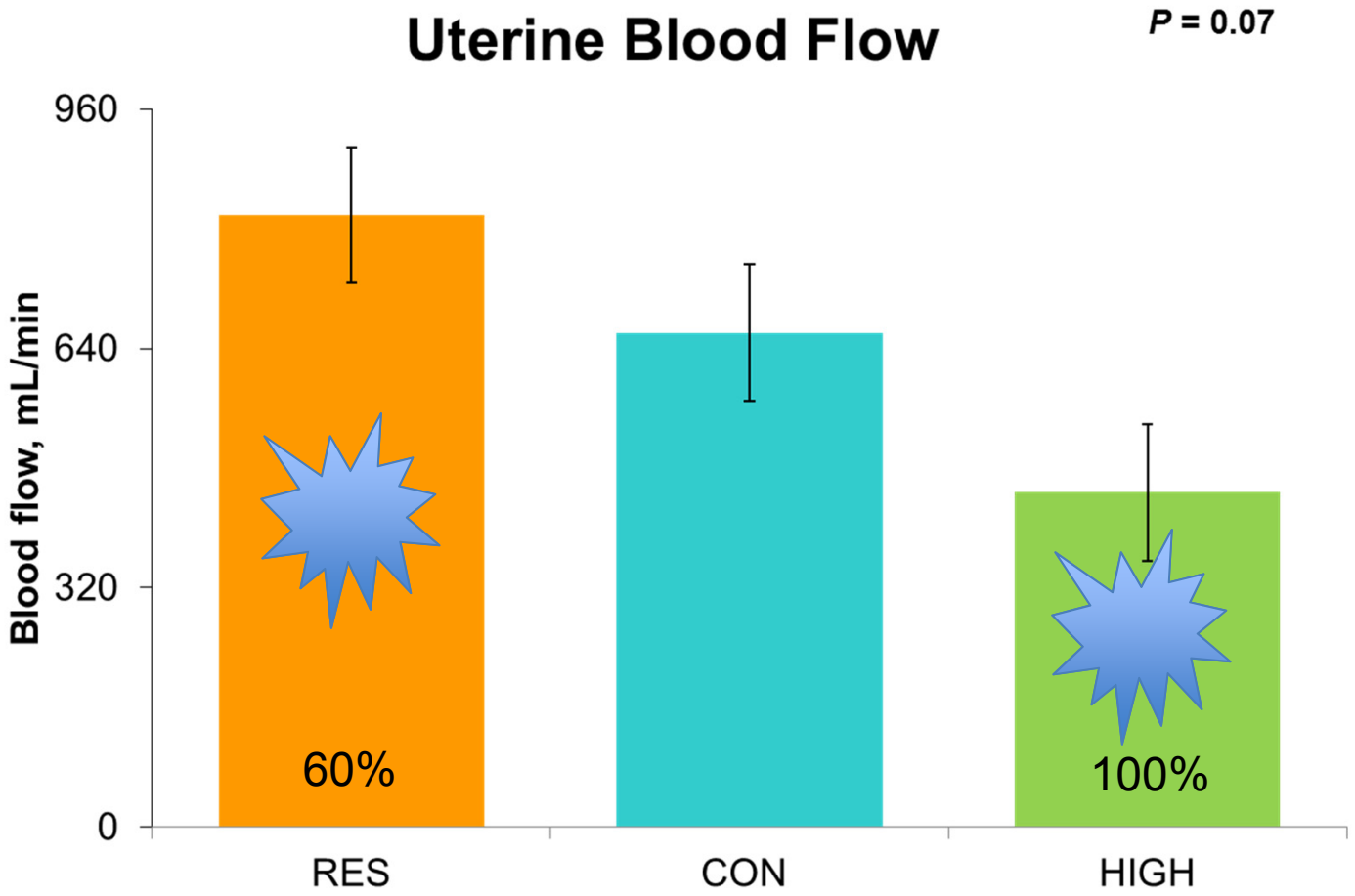


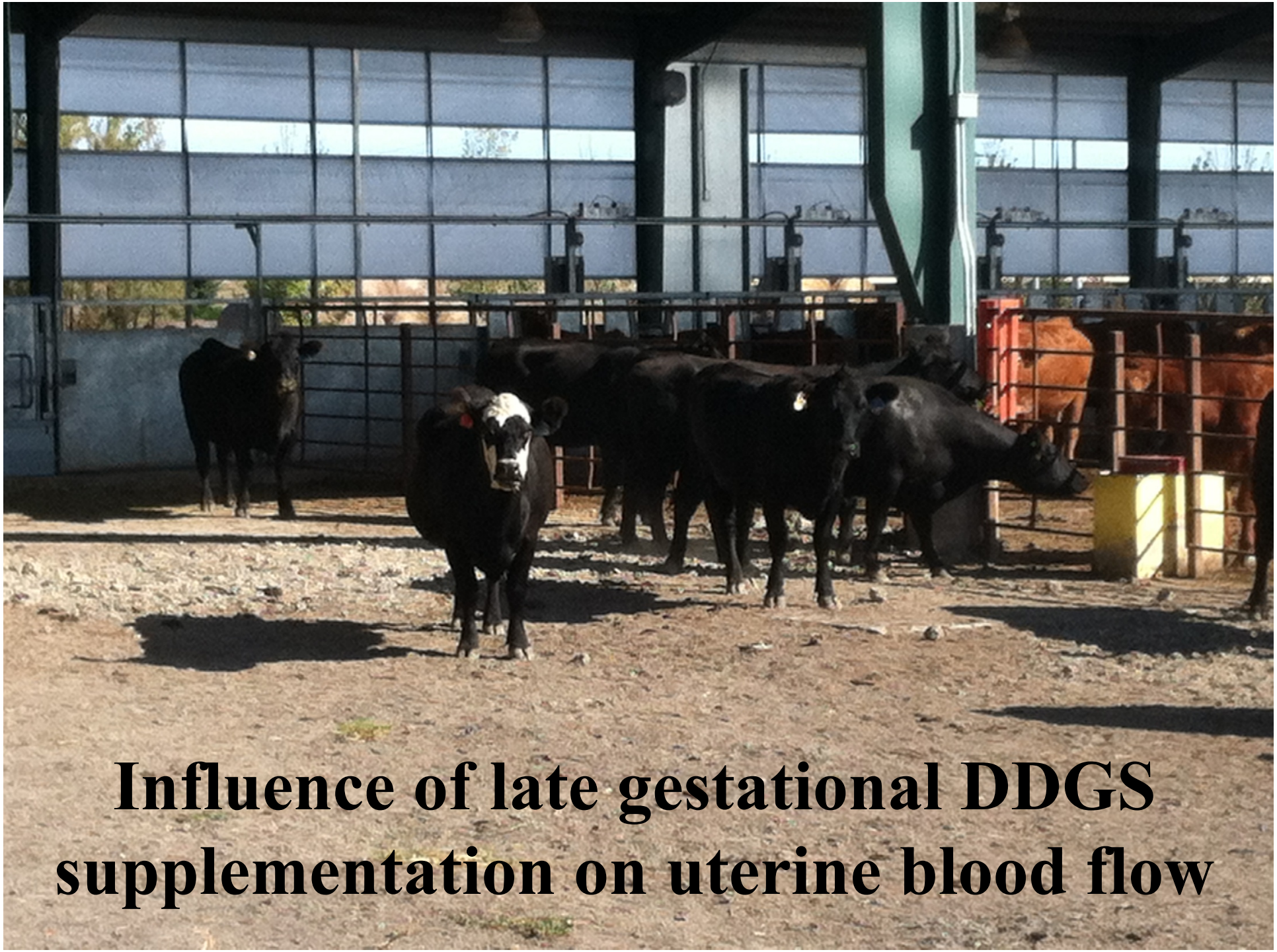
Results: COT DRCs

- Fetal placental arteries relaxed in the presence of inhibitors
  - Nonclassical mechanism?



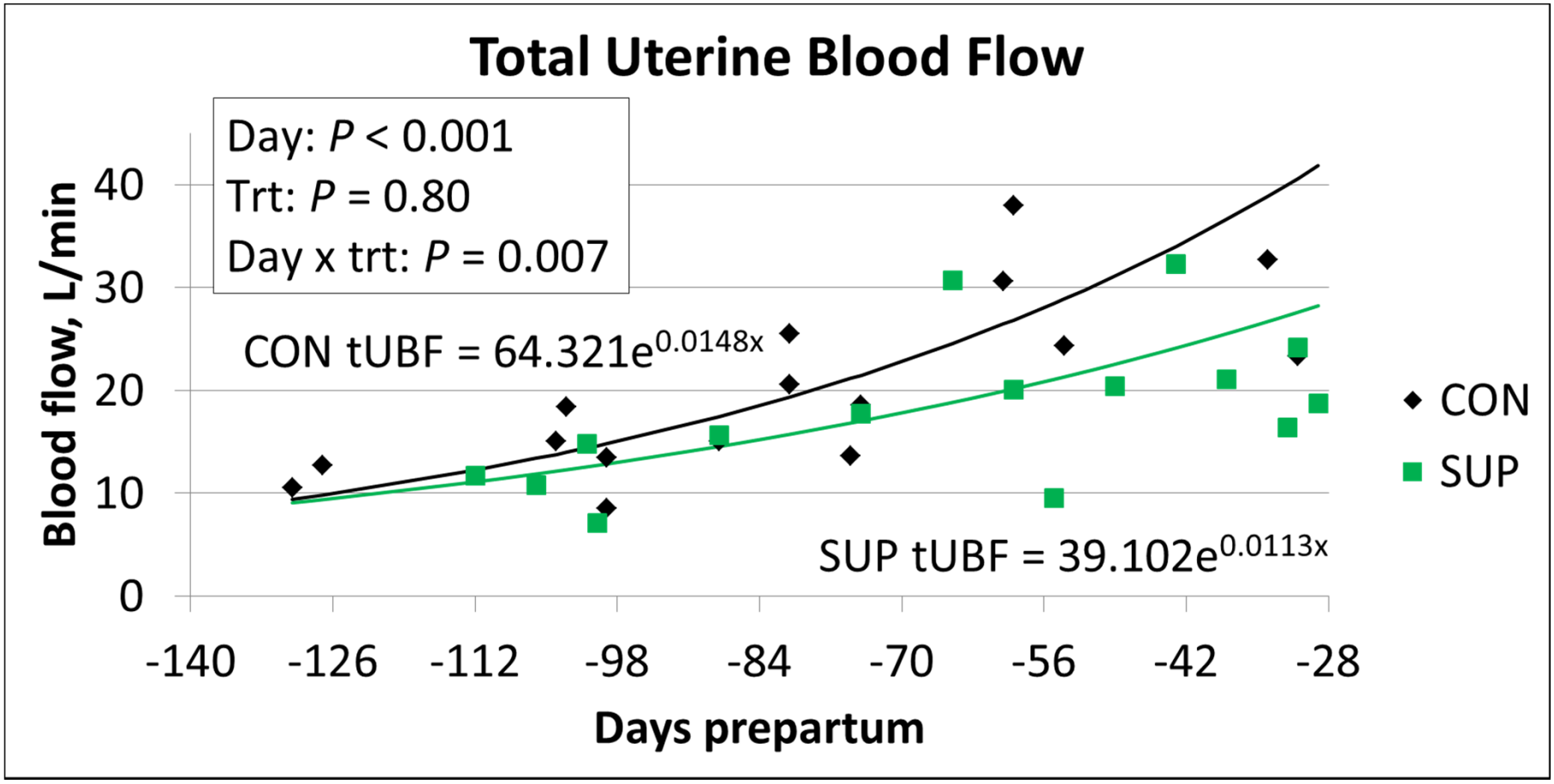
MP during Last Third of Gestation in Ewes





Influence of late gestational DDGS supplementation on uterine blood flow

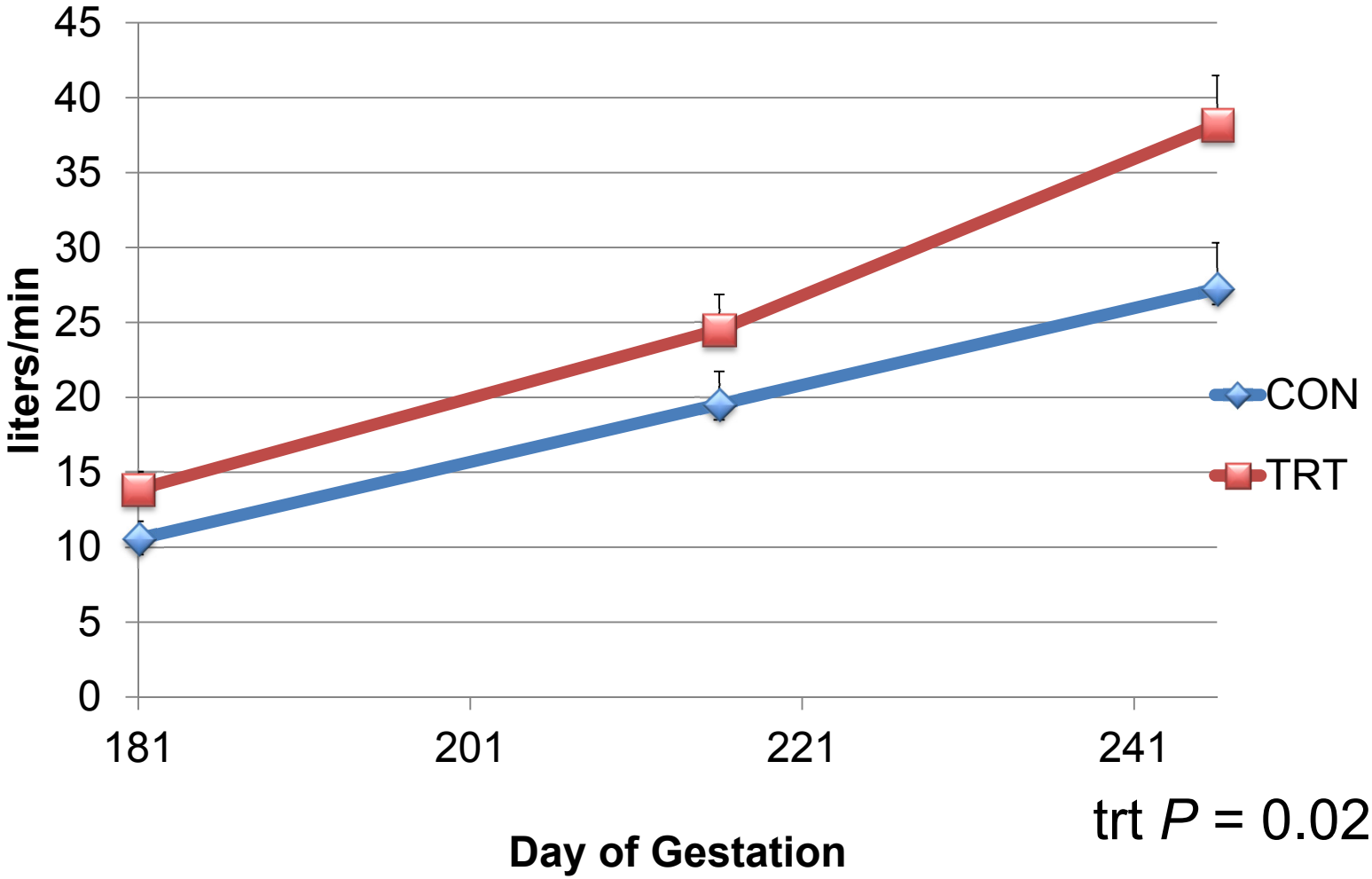
2012-2013 uterine blood flow



Mordhorst et al., unpublished data

Protein in 2013-2014

Total Uterine Blood Flow



Kennedy et al., unpublished data

Mechanisms for changes?

- In both species, protein did not impact placental weight
- BUT, perhaps change in function may be the key
- Steroid catabolism

Developmental Programming

- Placenta plays a key role in developmental programming
  - "Plastic"
  - Ability to compensate
  - Target for therapeutics

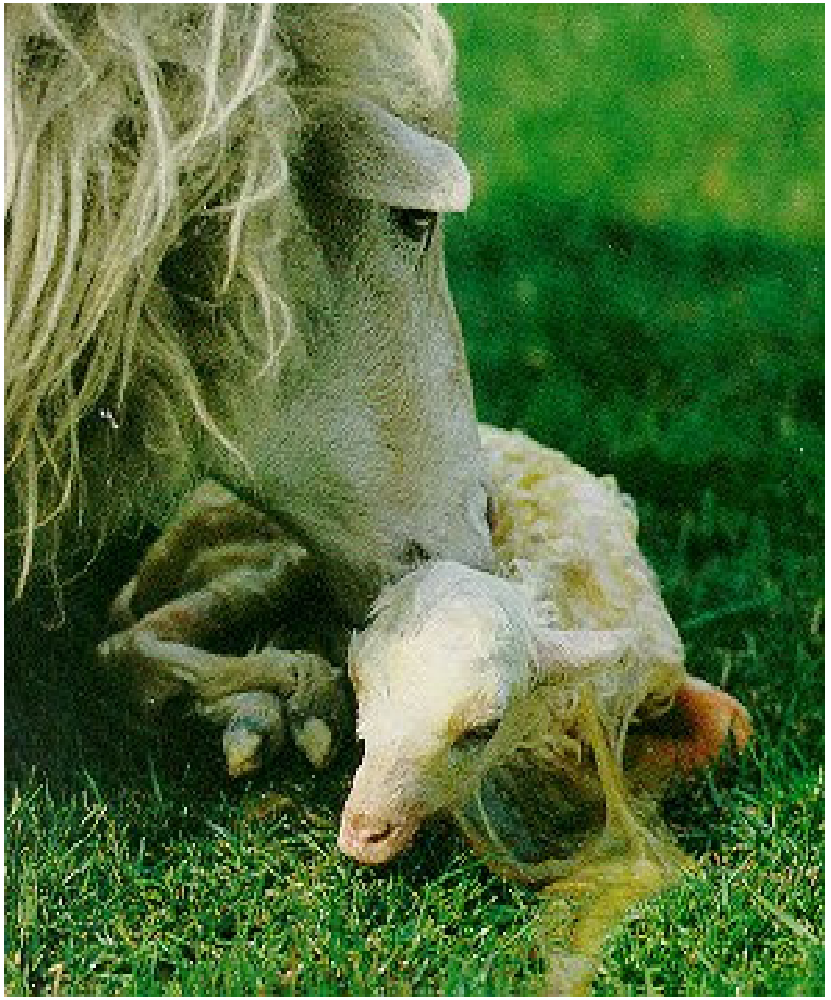
Future Directions

- Time period of supplementation
- Specific nutrients that are important
- Maternal efficiencies and maternal age
- Factors that impact
  - Uterine and placental blood flow
  - Mammary gland development

Developmental Programming

- IMPORTANT TO ANIMAL HEALTH AND PRODUCTIVITY:
  - Growth and nutrient transfer
  - Reproductive capacity
  - Aging and lifetime productivity

Goal: Healthy Offspring!!!

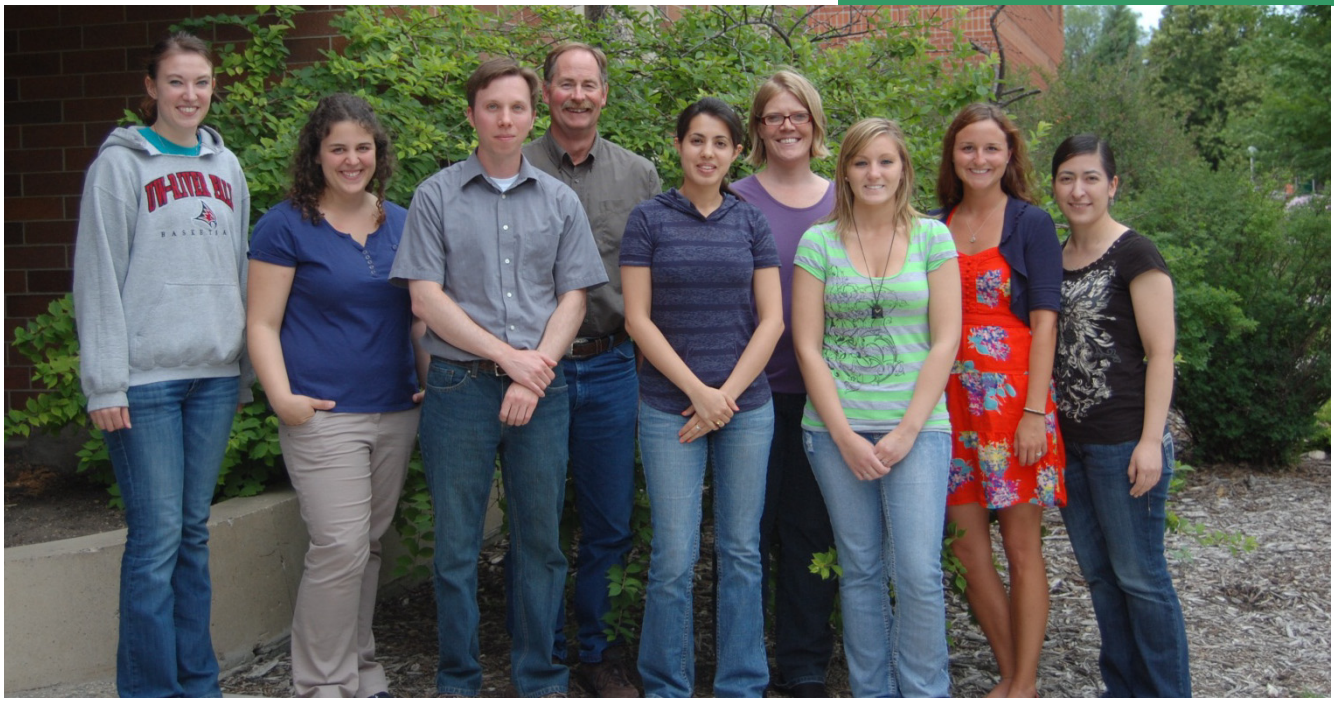


Goal: Healthy Offspring!!!

Acknowledgements

United States Department of Agriculture
National Institute of Food and Agriculture

NDSU Animal Nutrition and Physiology Center




ALOKA
N D S U
:No ID
PK-18dB
11.22.'13
14:52:47
↑3.35 80deg
1PI
PI: 0.756
RI: 0.519
PSV:310.7cm/s
EDV:149.4cm/s
MnV:213.3cm/s
FlowT: 1.52s
2PI
PI: 0.840
RI: 0.541
PSV:331.6cm/s
EDV:152.4cm/s
MnV:213.5cm/s
FlowT: 1.28s
PI
PI: 0.653
RI: 0.459
PSV:325.7cm/s
EDV:176.3cm/s
MnV:228.6cm/s
FlowT: 1.25s
4.30 G35 C11
Next
SEL ch
Locate
Menu
AutoT Smooth:NO
Clear
DUR:100%