Science, Religion, and Lunch Seminar

You are what your parents ate (and did)

Larry Reynolds, PhD
University Distinguished Professor of Animal Sciences

"Healthy Offspring through Optimal Nutrition"

Center for Nutrition and Pregnancy
North Dakota State University

STUDENT FOCUSED • LAND GRANT • RESEARCH UNIVERSITY

Science, Religion, and Lunch Seminar

Or, how Developmental Programming determines your health and well-being

Larry Reynolds, PhD
University Distinguished Professor of Animal Sciences

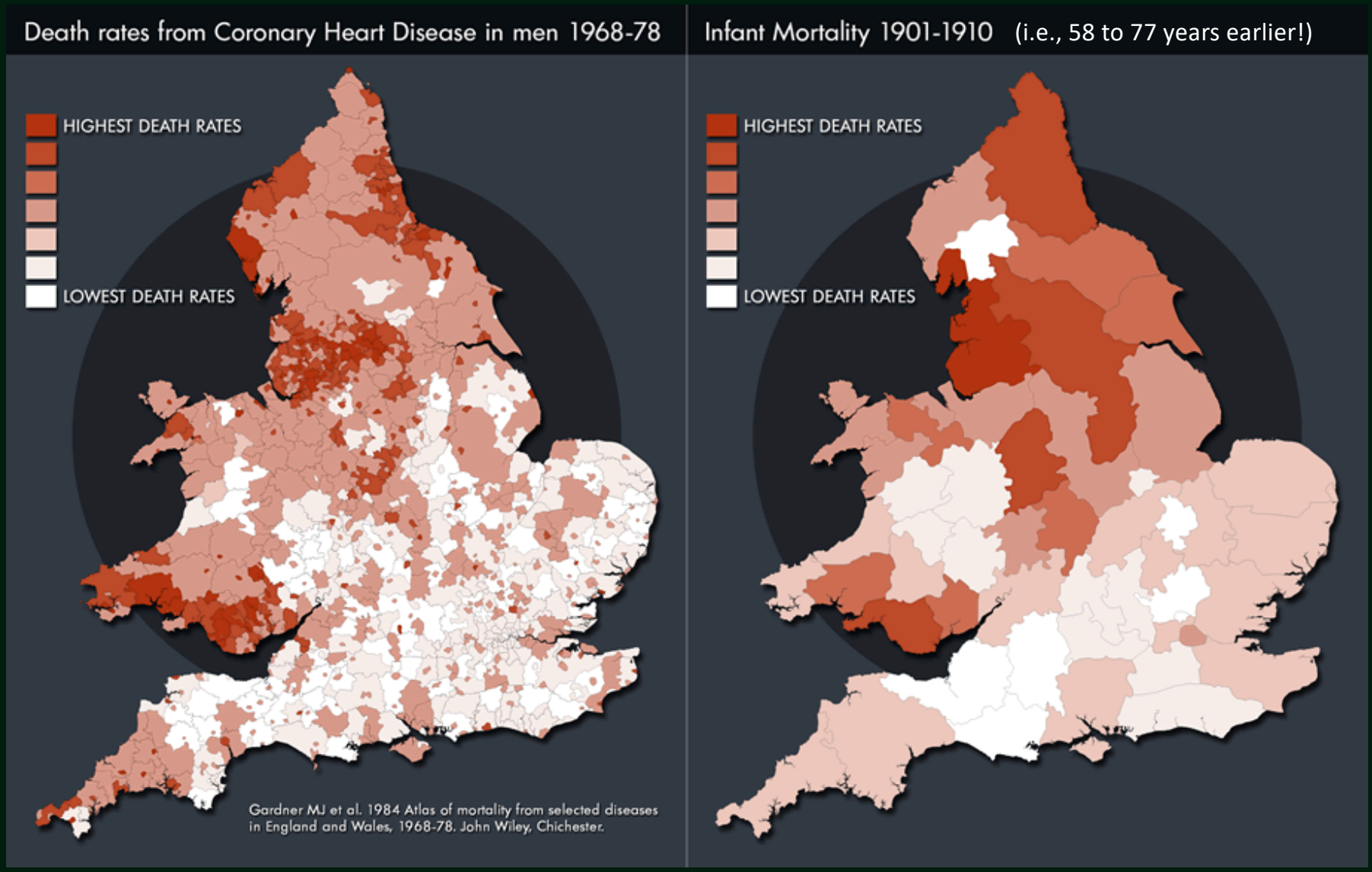
"Healthy Offspring through Optimal Nutrition"

Center for Nutrition and Pregnancy
North Dakota State University

STUDENT FOCUSED • LAND GRANT • RESEARCH UNIVERSITY

The Concept – Fetal, or Developmental, Programming

Center for Nutrition and Pregnancy



Data from Dr. David Barker

The Concept – Fetal, or Developmental, Programming

- Also termed the “Barker Hypothesis,” or ”Fetal Programming”
- Epidemiological evidence in humans, indicating that poor fetal growth and development affect newborns and infants

The Concept – Fetal, or Developmental, Programming

Center for Nutrition and Pregnancy

- Also termed the "Barker Hypothesis"
- Epidemiological evidence in humans, indicating that poor fetal growth and development affect newborns and infants **but also profoundly affect adult health and productivity (i.e., life-long consequences!)**

NDSU NORTH DAKOTA STATE UNIVERSITY

The Concept – Fetal, or Developmental, Programming

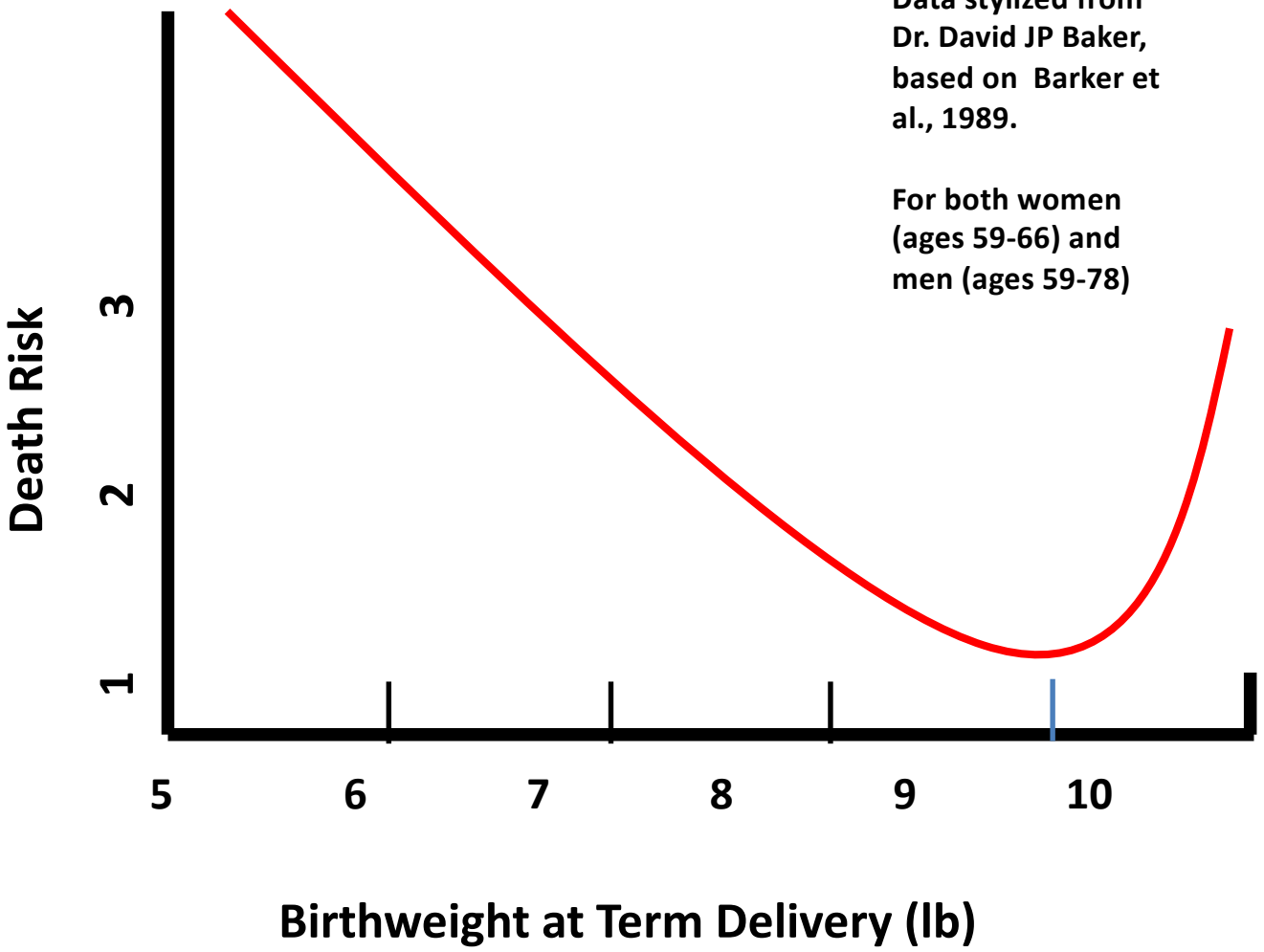
Center for Nutrition and Pregnancy

- Also termed the "Barker Hypothesis"
- Epidemiological evidence in humans, indicating that poor fetal growth and development affect newborns and infants **but also profoundly affect adult health and productivity (i.e., life-long consequences!)**
- The 'consequences' include a 3- to 10-fold increased risk of non-communicable diseases in the offspring as adults

NDSU NORTH DAKOTA STATE UNIVERSITY

Relative Risk of Death from Heart Disease Predicted from a Person's Birth Weight

Courtesy Dr. Kent Thornburg, Oregon Health Science Univ.



Center for Nutrition and Pregnancy

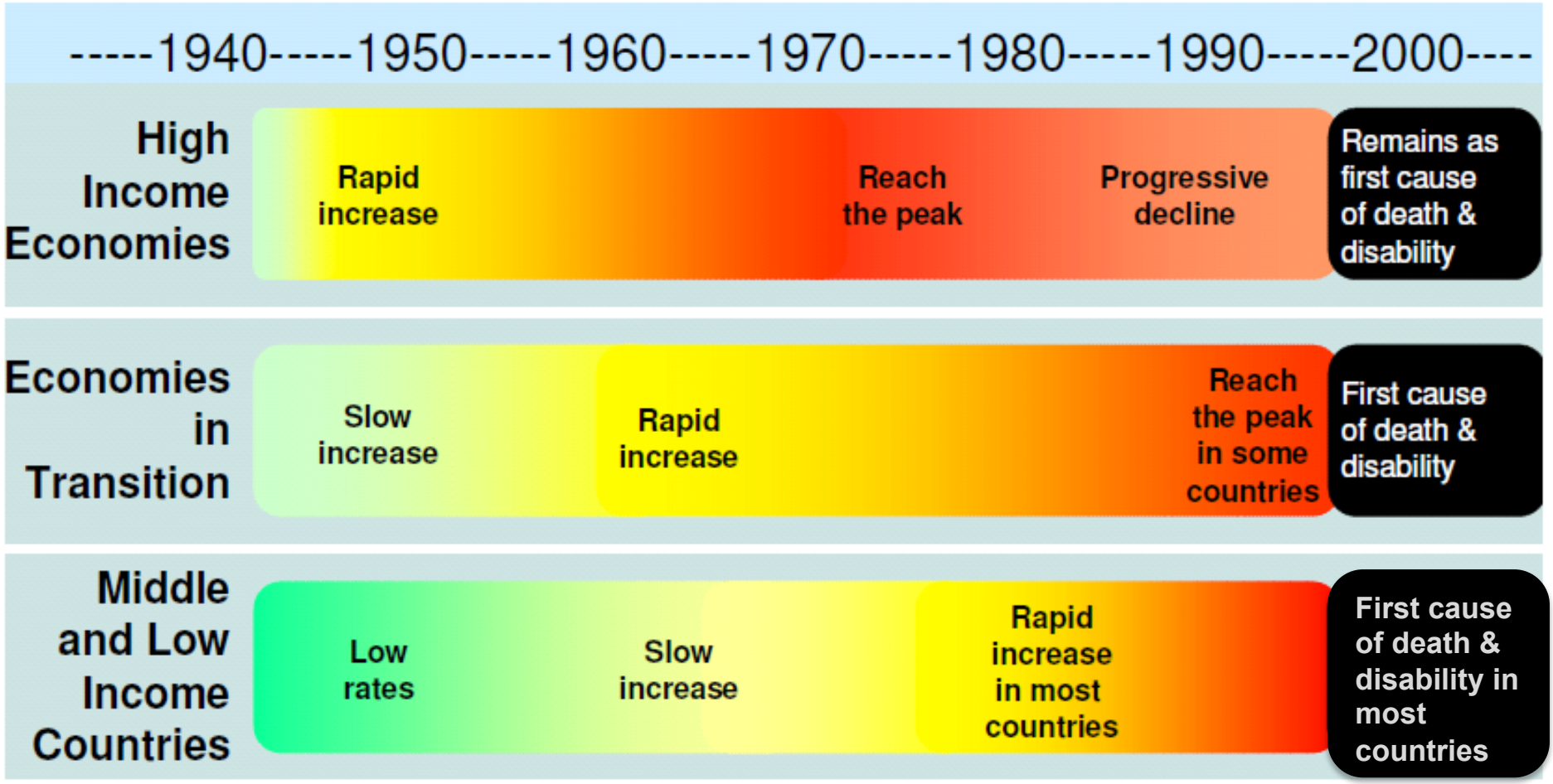
Non-Communicable Diseases – A Major Health Threat*

- In Sept. 2011, the UN convened a 'High Level Meeting' of member states:
  - Purpose was to address the global health threat of 'non-communicable diseases' (NCDs)
  - Only the second such meeting ever convened – first was in 2001 to address the global threat of AIDS
- Facts about NCDs (metabolic syndrome, cancer, autism spectrum disorders, depression, etc.):
  - In 2008, 36 million of the 57 million deaths (63%) worldwide due to NCDs
  - NCDs increasing rapidly in low-income countries
  - ¼ of deaths due to NCDs occur before age 60

NDSU NORTH DAKOTA STATE UNIVERSITY

*WHO Discussion paper, 2012 <www.who.int/nmh/events/2012/discussion_paper3.pdf>; D. E. Bloom *et al*., *The Global Economic Burden of Non-communicable Diseases* (World Economic Forum, 2011) <www.weforum.org/reports/globaleconomic-burden-non-communicable-diseases>

Cardiovascular (CVD) epidemic in countries of different stages of development



Source: WHO, NMH/MNC

Obtained for use from Magid Ezzati,Harvard

D. Yach – 4/13/09

Courtesy Dr. Kent Thornburg, Oregon Health Science Univ.

The Best Evidence for Developmental Programming!

Center for Nutrition and Pregnancy

- My mom smoked a pack a day
- My birth weight was approx. 4 lb 6 oz (2.0 kg)
  - Well below the universal cutoff for low birth weight
  - Still, I am average height and weight (5' 11", 185 lb)
  - My wife, Kay, is 5'9" (a little above average height)
- My boys (Shaun, 34 and Scott, 30) received good nutrition while in utero
  - No smoking or drinking for either pregnancy
  - Both had normal birth weights (approx. 7½ lb)

NDSU NORTH DAKOTA STATE UNIVERSITY

The Best Evidence for Developmental Programming!

Center for Nutrition and Pregnancy

NDSU NORTH DAKOTA STATE UNIVERSITY

Center for Nutrition and Pregnancy

Developmental Origins of Health and Disease – Some Research Observations

- Results from poor maternal diet, multiple fetuses, maternal stress, maternal age, etc.
- Occurs in many mammals based on epidemiology (primarily humans) and controlled studies (animals)
- Is often (but not always) reflected by low birth weight
- Affects nearly every major organ system (both structure and function) and bodily process
- Critical 'windows' for Developmental Programming include not only the fetal period but also infancy (birth to 1 yr of age)

NDSU NORTH DAKOTA STATE UNIVERSITY

*Wu et al., J Anim Sci 84:2316-37, 2006; Reynolds et al., J Anim Sci. 88(Suppl. 13):E61-E72, 2010, & J Develop Biol 54:355-366, 2010; Reynolds and Caton, Molec Cell Endocrinol 354:54-9, 2012.

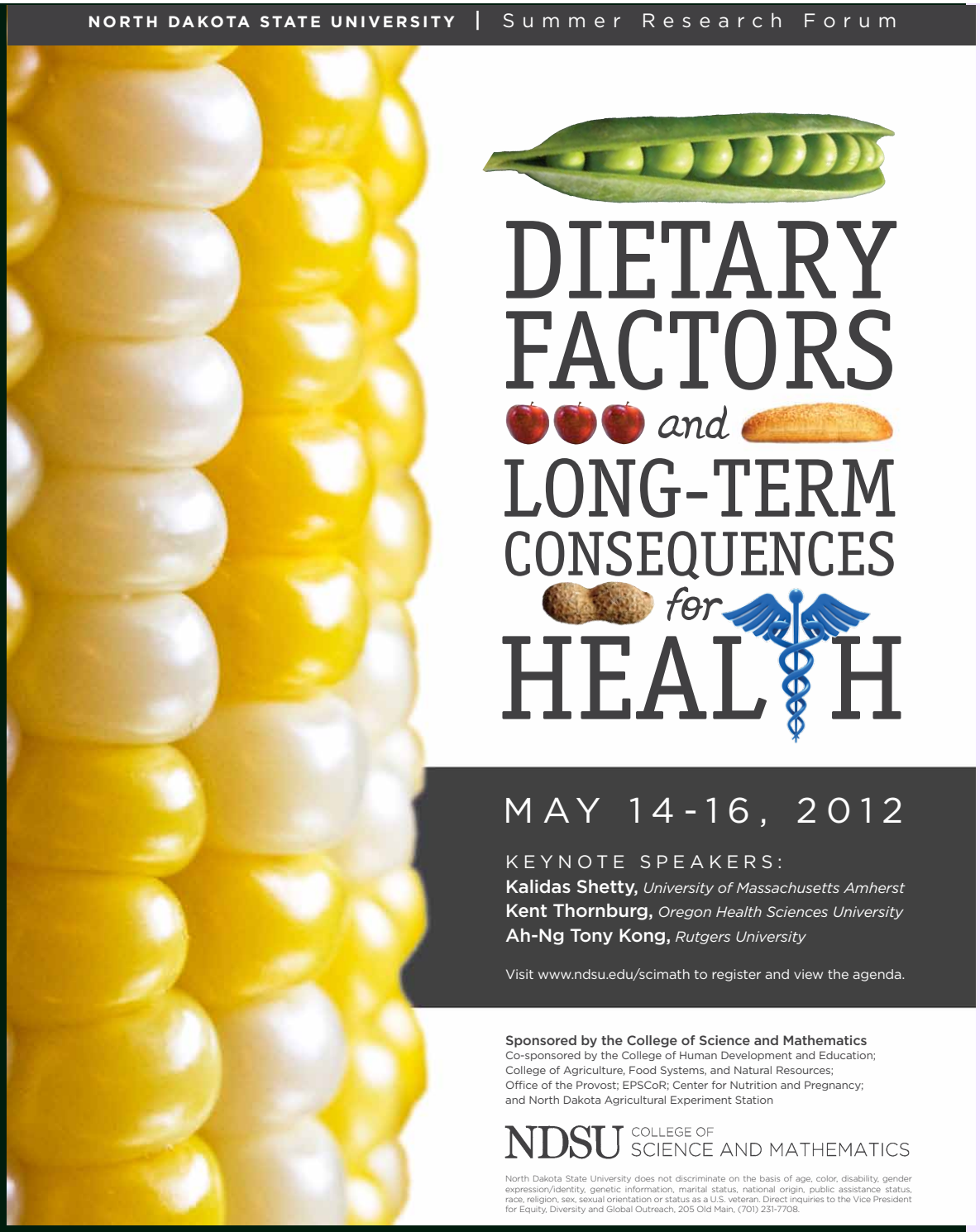
Developmental Programming and Adult Health in the Media

Center for Nutrition and Pregnancy

September 27, 1999

December 10, 2007

Pregnancy, 28 January 2020, pg. 13



- Challenge: to 'integrate' food sciences and sciences into 'health sciences'
  - Use animal models of 'healthy lifestyle' with focus on non-communicable diseases
  - Animal-based foods as part of healthy lifestyle
- Opportunity: to return public appreciation of animal-based foods as part of a healthy lifestyle – will take a concerted effort among scientists, funding entities, and policy-makers!

© Lawrence P. Reynolds, PH.D., January 20, pg. 14

Animal Frontiers, Vol. 9, October 2019

Guest Editor:
Eric Berg, PhD
Professor
Animal Sciences
NDSU

Why Study Compromised Pregnancy?*

- Compromised pregnancy = any pregnancy in which fetal or placental growth, or both, are abnormal
- Abnormal birth weight in humans:
  - Is a major factor contributing to high infant (birth to 1 year of age) mortality rates
    - > 0.7% infant mortality in the U.S., which the highest in the developed world
    - As high as 16.5% infant mortality in some developing countries; 1.8% in China
  - Is a major cause of 'Developmental Programming' of the offspring, resulting in a 3x to10x increase in the rates of so-called 'non-communicable diseases' (cardiovascular disease, diabetes, obesity, cognitive dysfunction, etc.), as adults

*MDG 4, Child mortality, Infant mortality rate. Global Health Observatory Database, WHO , 2008: http://apps.who.int/ghodata/; Godfrey and Barker, , Am J Clinical Nutr, 71:1344S-52S, 2000

FELLOWSHIP of THE RING
Fighting Darkness through Hope, Courage, and Luck!

Top, left to right – Arwen, Aragorn, Frodo, Gandalf, Legolas
Bottom, left – The 3 Hobbit Companions – Pippin, Sam, and Merry

©Pinterest.com

FELLOWSHIP of FERTILITY

Fighting Problems of Pregnancy through Science (and Hope, Courage, and Luck!)

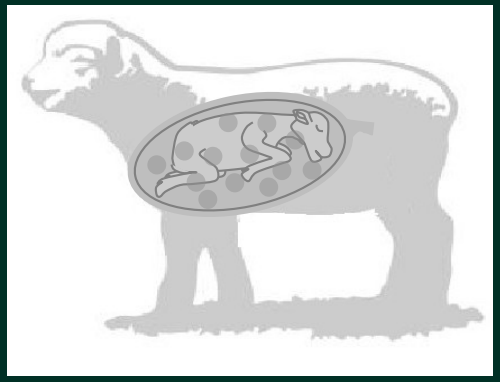
Top, left to right – Drs. Alison Ward, Carl Dahlen, Joel Caton, me, Pawel Borowicz
Bottom, left – Undergrad & Grad Students and Postdocs!

©Pinterest.com

Sheep as a Model for Compromised Pregnancy*

Center for Nutrition and Pregnancy

- Like all placental mammals, there is an absolute dependence of pregnancy on progesterone, and a similar profile of pregnancy hormones
- Primarily singleton and twin pregnancies, and extended gestation length (approx. 145 days)
- Large amounts of tissue available, and can chronically instrument mother and fetus
- Structure and function of placental vessels in sheep and humans is similar
- Ability to examine multiple stages of gestation, and well-known physiology
- Compromised pregnancies exhibit complications similar to those of humans



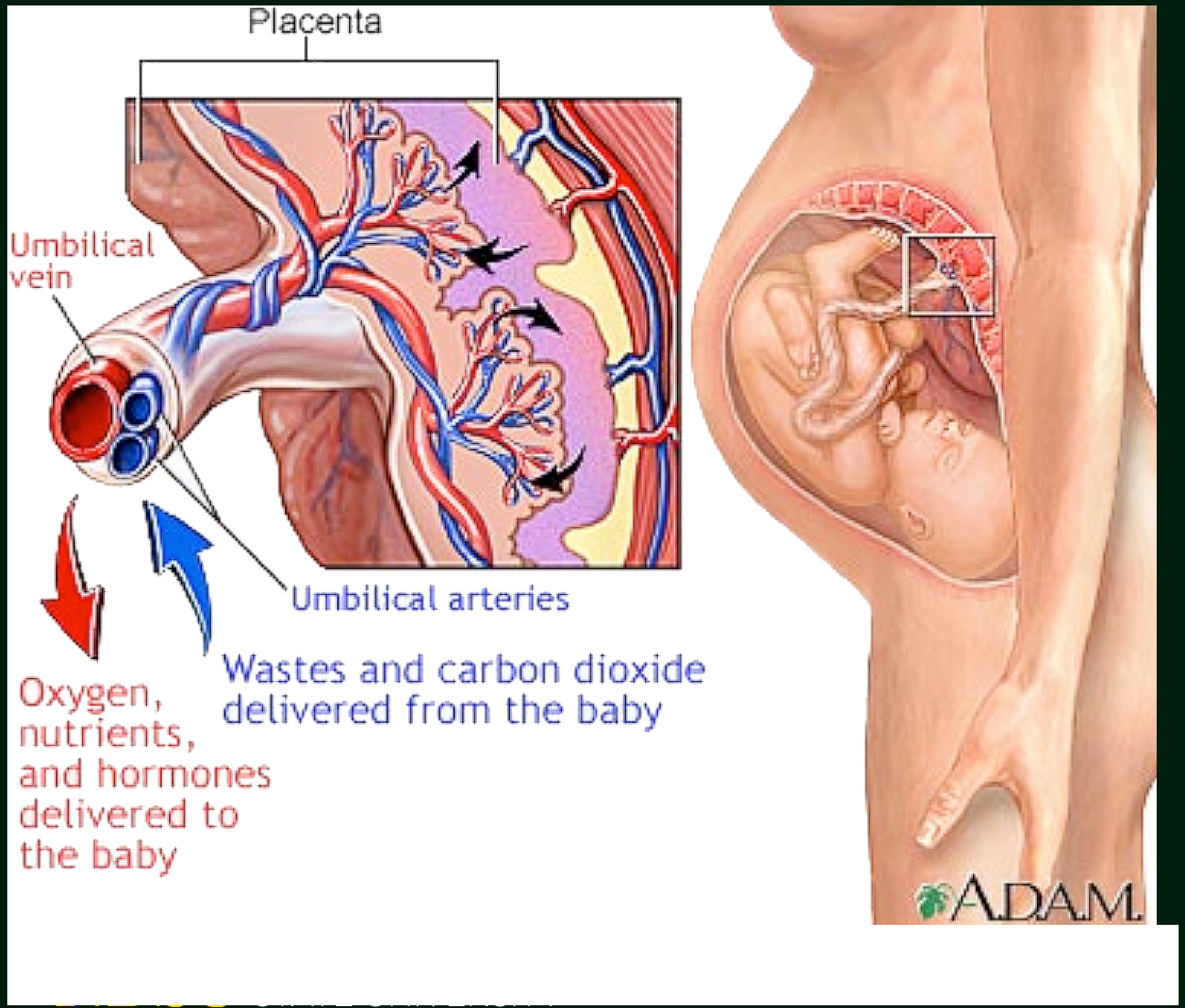
NDSU NORTH DAKOTA STATE UNIVERSITY

*Wallace et al., J Physiol 565.1: 19-26, 2005; Reynolds et al, J Anim Sci 88(E Suppl):E61-E72, 2010

© Lawrence P. Reynolds, PH.D., January 20, pg. 19

Center for Nutrition and Pregnancy

Why Study the Placenta in Compromised Pregnancies?*



Fetal Nutrient Transport is Exclusively via the Placenta!

Center for Nutrition and Pregnancy

Why Study the Placenta in Compromised Pregnancies?*

- Factors that negatively affect fetal growth and development **also impact the placenta**, causing:
  - Reduced placental growth, resulting in small placental size
  - Altered placental function (more on this in the next slide)
- These factors include:
  - Maternal nutritional stress
  - Multiple fetuses
  - Maternal age
  - Maternal environmental stress (e.g., high altitude, heat stress, relational stress)
  - Maternal and fetal ethnicity

NDSU NORTH DAKOTA STATE UNIVERSITY

*Reynolds and Redmer, J Anim Sci 73:1839-1851, 1995; Reynolds et al., Int. J. Develop. Biol. 54:355-366, 2010.

Reduced Placental Blood Flow/Vascularity in Compromised Pregnancy in Sheep*

Center for Nutrition and Pregnancy

Model	Fetal Wt	Placental Wt	Placental Vascularity	Gravid Ut Blood Flow	Umbilical Blood Flow
Overfed Adolescent	- 20-40%	- 20-45%	- 31%	- 36%	- 37%
Multiple Pregnancy	- 30%	- 37%	- 30%	- 23%	---
Heat-Stressed Adult	- 42%	- 51%	---	- 26%	- 60%
Underfed Adult	- 12%	---	- 14%	- 25%	NSE
Underfed Adolescent	- 17%	NSE	- 20%	---	---
Adolescent vs. Adult	- 16%	- 26%	- 24%	---	---
Maternal Genotype (Adult only)	- 44%	-28%	- 33%	---	---

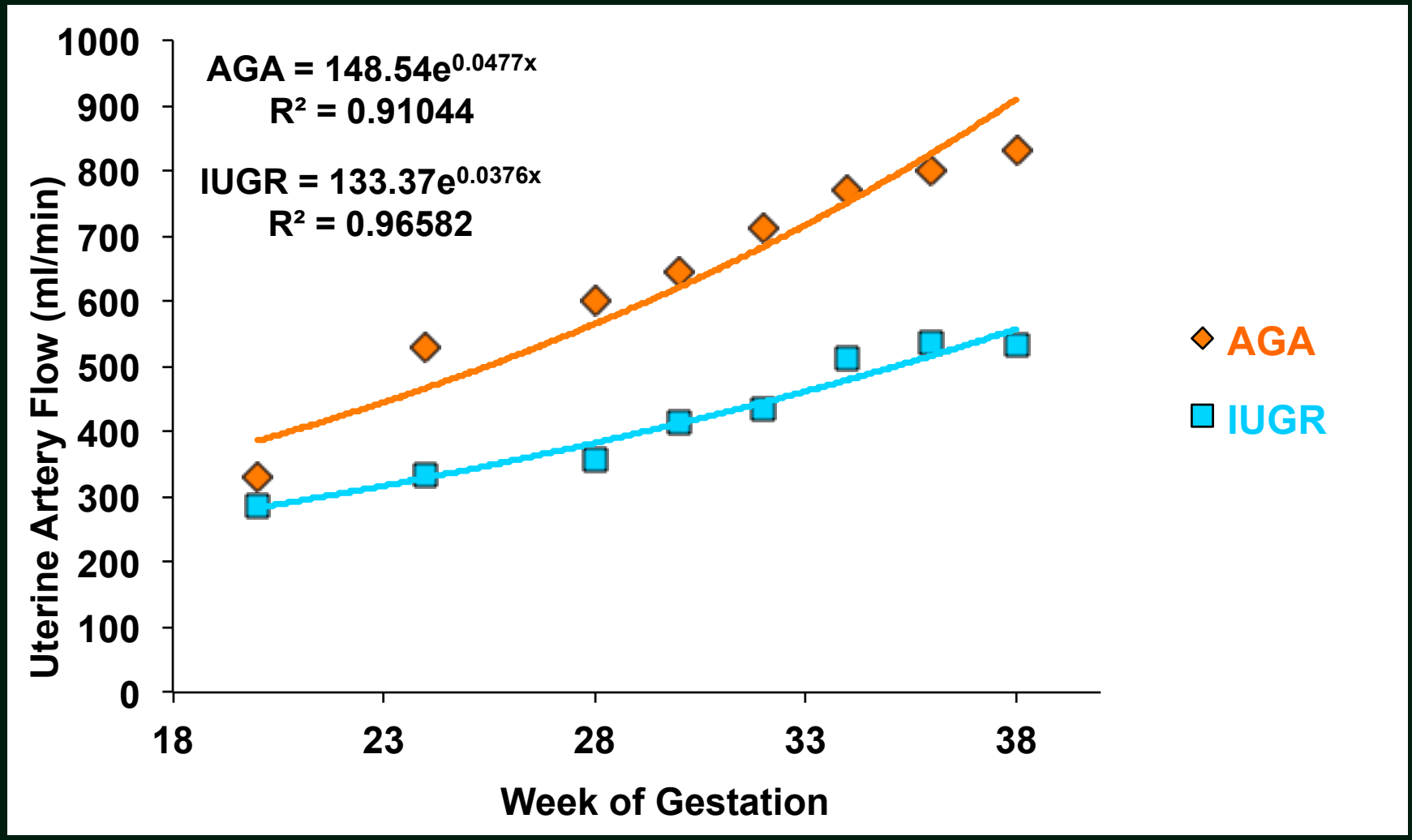
Note that the large increase in placental blood flow during pregnancy depends on growth of the placental vascular beds; i.e., **placental angiogenesis**

NDSU NORTH DAKOTA STATE UNIVERSITY

*Reynolds et al, J Physiology 572.1:51-58, 2006

Uterine Artery Blood Flow in Normal and Growth-Restricted Human Pregnancies*

Center for Nutrition and Pregnancy



NDSU NORTH DAKOTA STATE UNIVERSITY

*Konje et al, Brit J Obstet Gynecol 110:301-5, 2003

Placental Vascular Development in Human IUGR*

Center for Nutrition and Pregnancy

Table 1. Growth measures (volumes, cm^3; surface areas, m^2; lengths, km) of peripheral villi and fetal capillaries. Values are group m

↓ 40-50%

Variable	Controls		IUGR	PE + IUGR
Villous volume[a]	219 (19)	179 (17)	130 (25)	105 (20)
Villous surface[a]	11.1 (0.67)	9.38 (0.18)	6.63 (1.47)	5.23 (1.07)
Villous length[a]	60.6 (6.75)	45.3 (3.58)	30.9 (7.02)	26.7 (4.93)
Capillary volume[a]	65.5 (8.71)	46.9 (3.53)	35.3 (8.65)	28.0 (6.91)
Capillary surface[a]	10.8 (1.40)	8.22 (0.81)	5.42 (1.40)	3.77 (0.75)
Capillary length[a]	233 (33)	172 (8.7)	110 (28)	90 (22)

[a]Significant effect of IUGR. No other effects were detected.

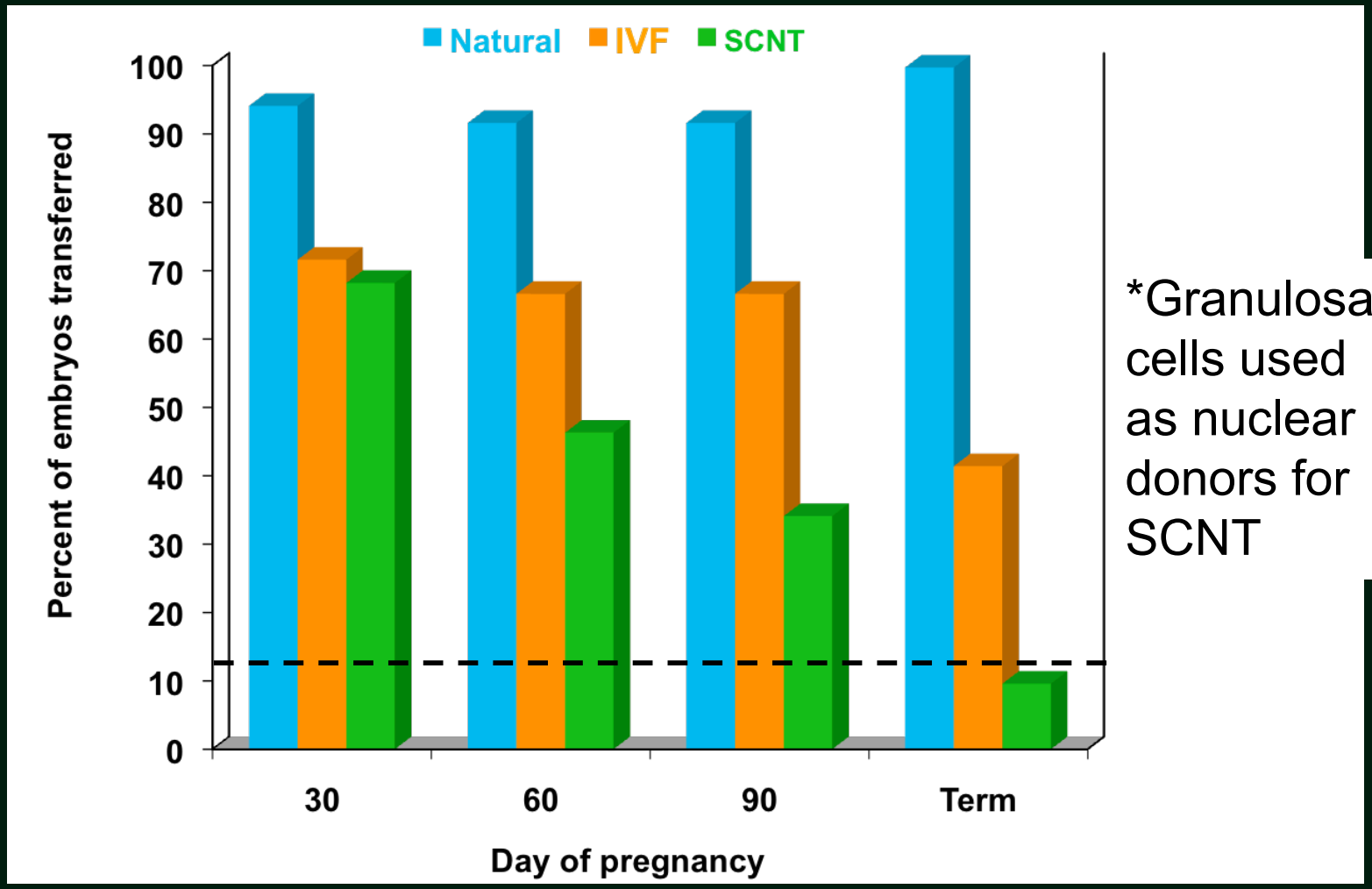
*All placentas from term (GA: Controls, 39±0.5; PE, 36±1.5; IUGR, 37±0.8; and PE+IUGR, 33±1.7 weeks);

NDSU NORTH DAKOTA STATE UNIVERSITY

Mayhew et al, Placenta 24:219-226, 2003; 25:829-833, 2004; 25:127-139, 2004 **Review**

Survival of In Vitro-Produced Embryos after Transfer in Sheep*

Center for Nutrition and Pregnancy



*Granulosa cells used as nuclear donors for SCNT

NDSU NORTH DAKOTA STATE UNIVERSITY

*Loi et al., 2006

Center for Nutrition and Pregnancy

Assisted Reproductive Technologies (ART) in Humans*

- Non-donor eggs only (88% of ART cycles)
- 146,244 ART cycles in the 441 fertility clinics (of 484 total in U.S.) reporting in 2009
- From 2000 to 2009 use of ART in the U.S. increased by 50% and number of ART-conceived births almost doubled (35,025 to 60,190)
- ICSI currently accounts for >70% of ART procedures in the U.S.
- ART-born babies account for 1% of all births (1.7% in the UK and 2.3% in the Netherlands) and 18% of multiple births in the U.S.
- Multiple-birth infants have increased risk of low birth weight, preterm delivery, and infant death
- But ART-conceived singletons also have increased risk of low birth weight, preterm delivery and fetal growth restriction and, possibly, long-term health problems

NDSU NORTH DAKOTA STATE UNIVERSITY

*Centers for Disease Control: (1) Assisted Reproductive Technology Reports, National Summary, 2009: http://apps.nccd.cdc.gov/art/Apps/Marquee.aspx and (2) Outline for a National Action Plan for … Management of Infertility, 2010; Williams & Sutcliffe, Early Human Develop 2009, 85:673-677; Gluckman & Hanson, Science 2004 ;305:1733-1736.

Center for Nutrition and Pregnancy

Assisted Reproductive Technologies (ART) in Humans*

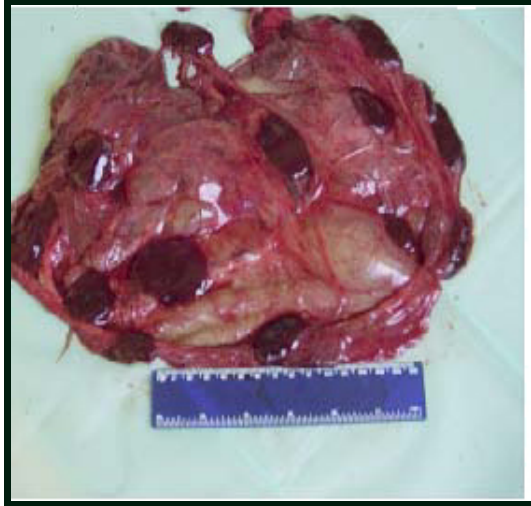
Item	All Ages Combined (<35-44)	
	Fresh Embryos	Frozen Embryos
Live births, % of transfers	36.6	30.8
No. of embryos transferred	2.1	2.2
No. of transfers	84,039	21,610

NDSU NORTH DAKOTA STATE UNIVERSITY

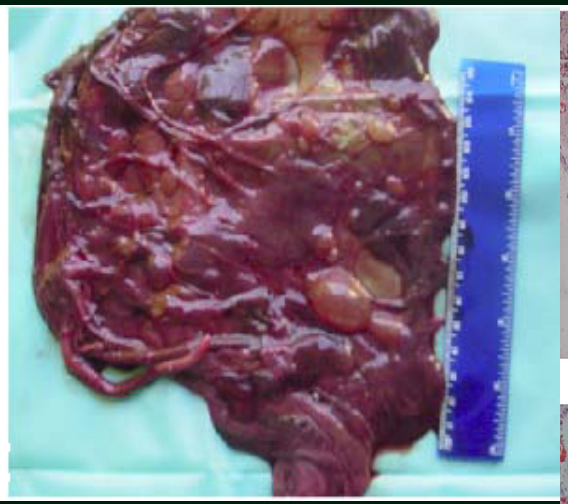
*Centers for Disease Control: (1) Assisted Reproductive Technology Reports, National Summary, 2009: http://apps.nccd.cdc.gov/art/Apps/Marquee.aspx and (2) Outline for a National Action Plan for … Management of Infertility, 2010; Williams & Sutcliffe, Early Human Develop 2009, 85:673-677; Gluckman & Hanson, Science 2004 ;305:1733-1736.

Compromised Vascular Development of the Placenta in Clones*

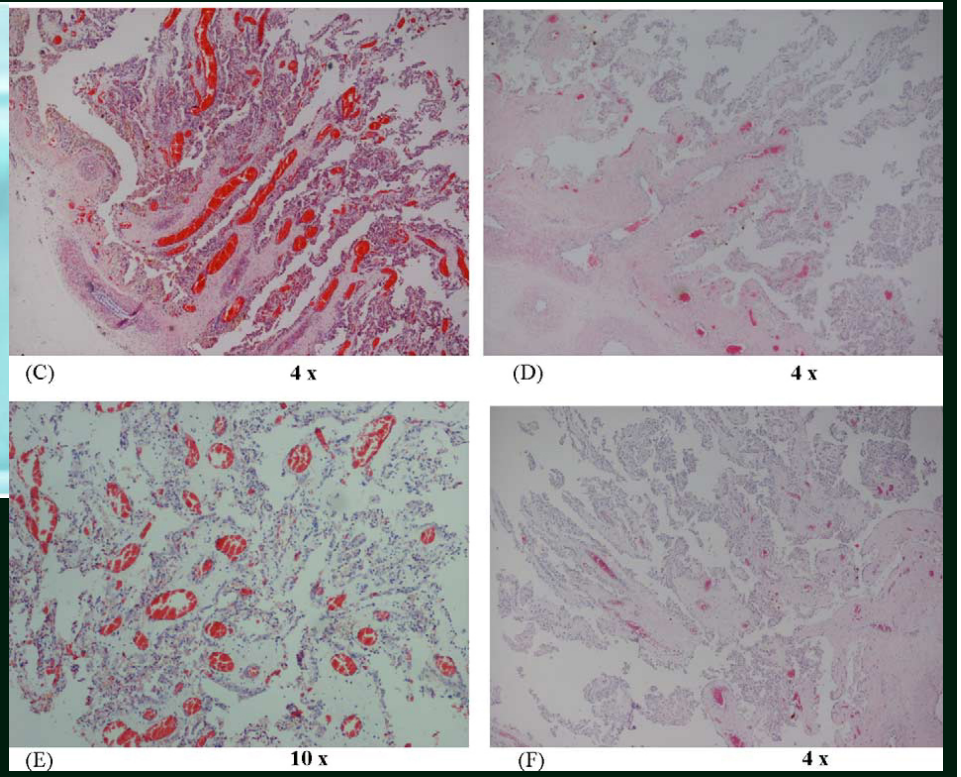
Center for Nutrition and Pregnancy



Normal



Cloned



Normal Cloned

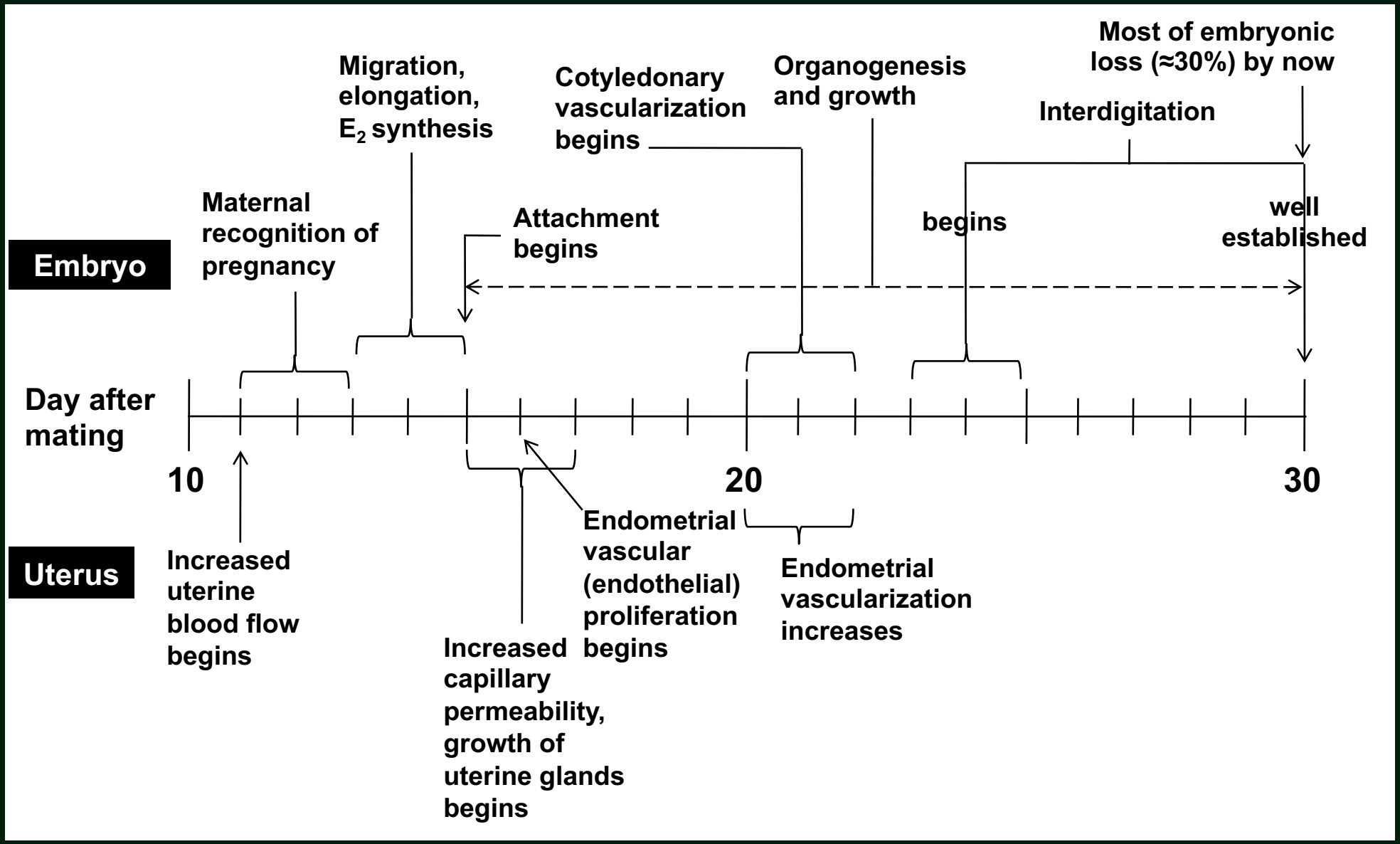
- All placentas from delivery; hematoxylin and eosin staining
- Poor vascularization of cloned placenta
- Trophoblastic degeneration of cloned placenta
- Increased thickness of placental basement membranes

NDSU NORTH DAKOTA STATE UNIVERSITY

*Palmieri, Loi, Reynolds, Ptak, Della Salda, 2007, Placenta 28:577-84

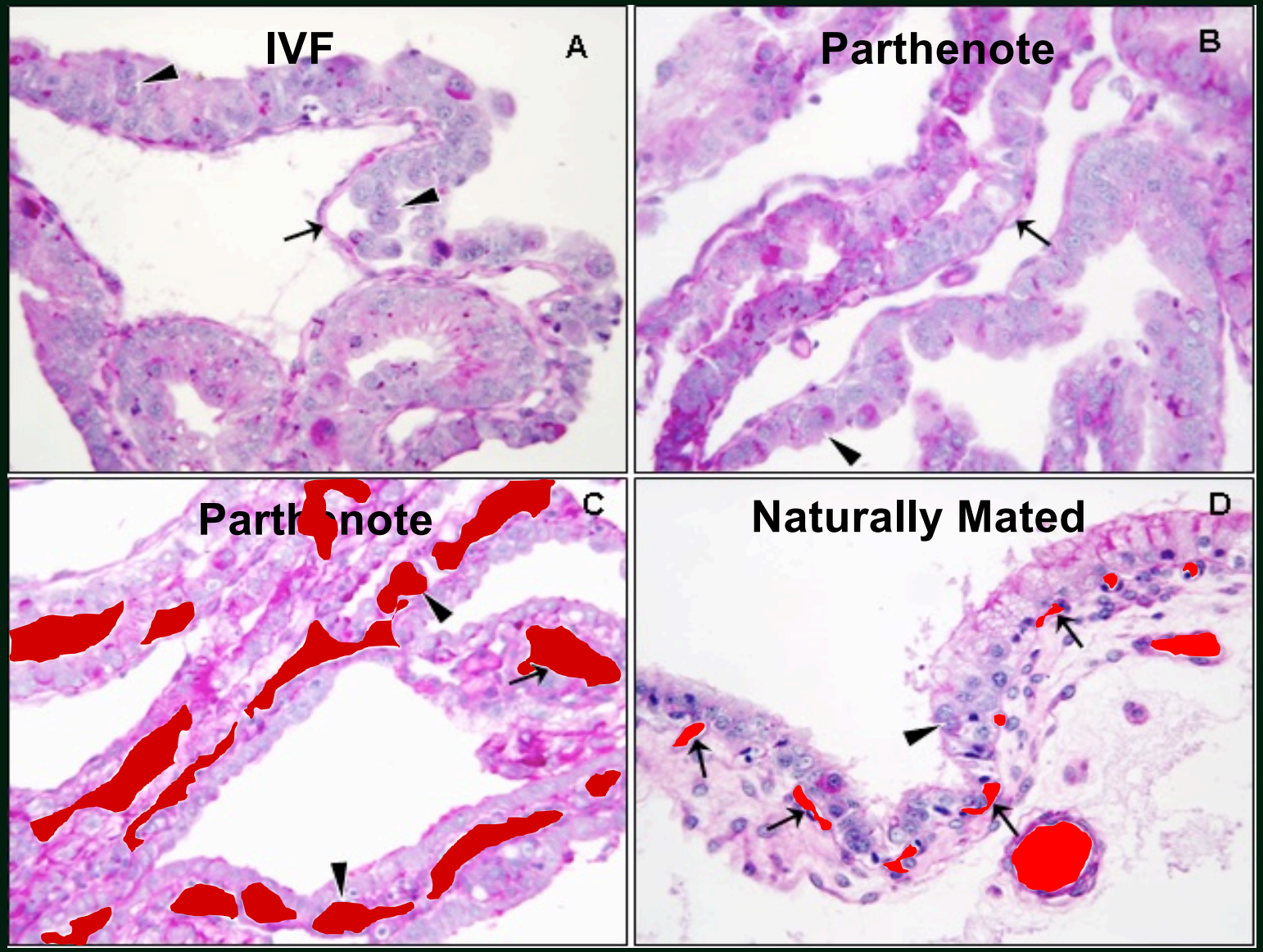
Timeline of Early Pregnancy in Sheep – A Critical Period*

Center for Nutrition and Pregnancy



Center for Nutrition and Pregnancy

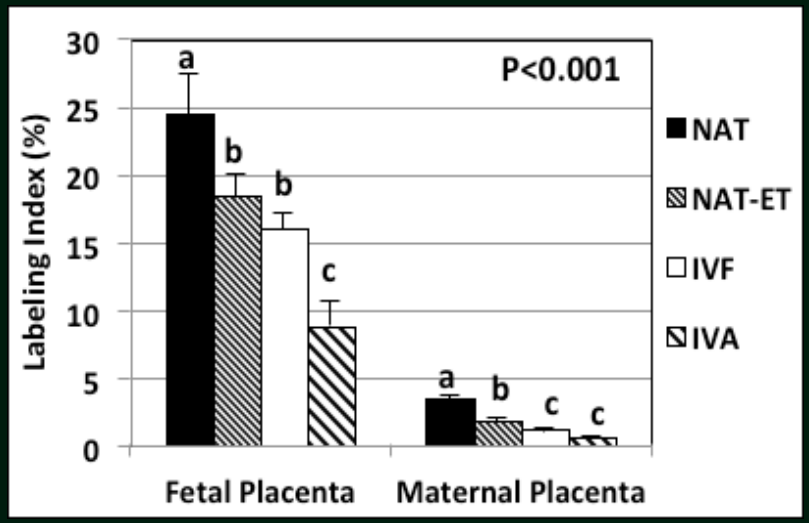
Placental Vascular Development in Early Pregnancy in Sheep Clones*

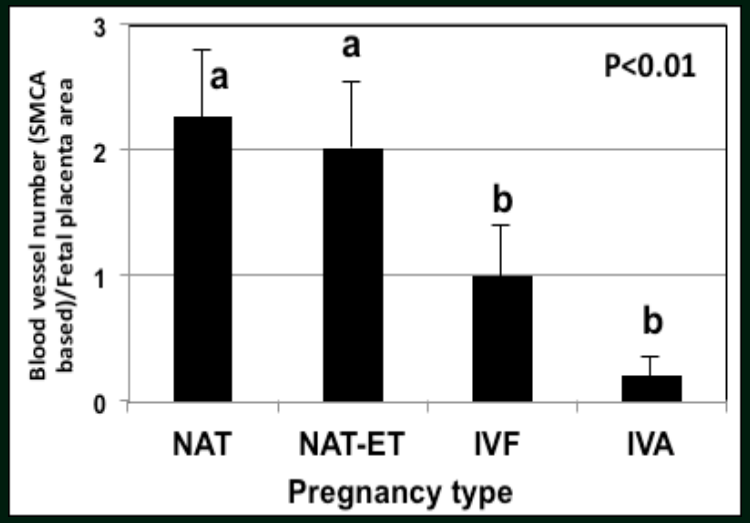


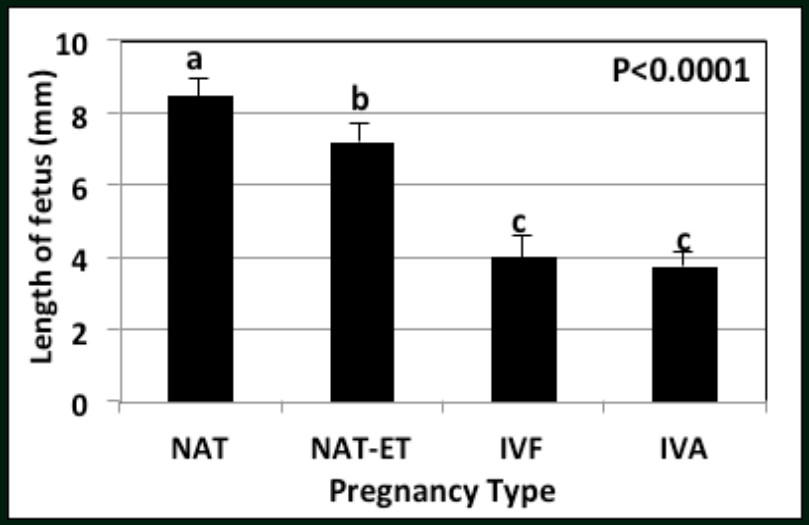
- All embryos from day 24
- Parthenote = in vitro-activated = clone w/ maternal genes only
- In embryos from IVF and Parthenotes, trophoblastic and vascular development is abnormal

Center for Nutrition and Pregnancy

Placental Vascular Development in Early Pregnancy in Sheep Clones*







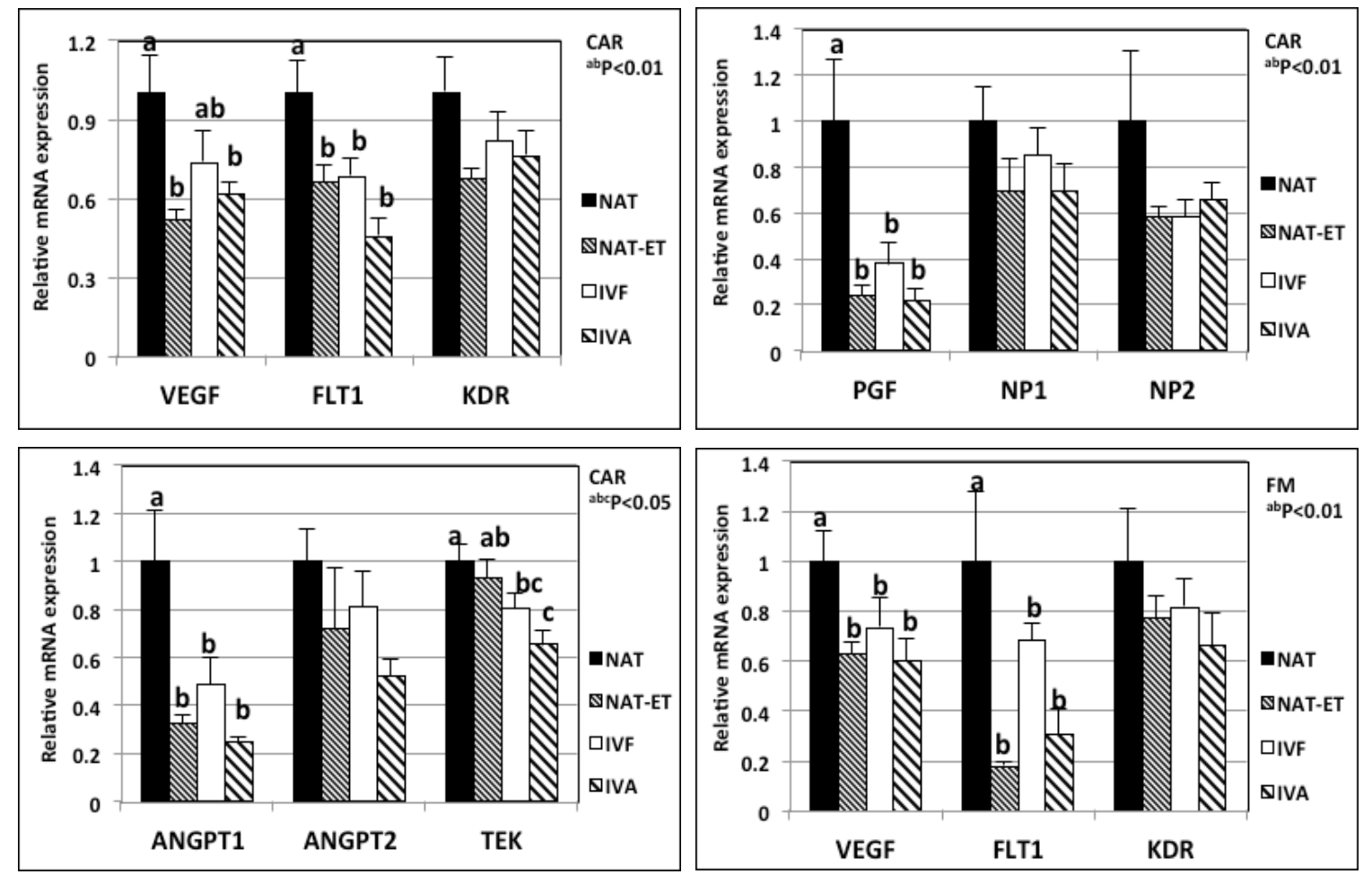
*All tissues collected on d 20-22 post-mating

NDSU NORTH DAKOTA STATE UNIVERSITY

*Grazul-Bilska et al, Repro-duction 140:165-174, 2010, and141:529-540, 2011, and unpubl.

Center for Nutrition and Pregnancy

Placental Vascular Development in Early Pregnancy in Sheep Clones*



*All tissues collected on d 20-22 post-mating

NDSU NORTH DAKOTA STATE UNIVERSITY

*Grazul-Bilska et al, Repro-duction 140:165-174, 2010, and141:529-540, 2011, and unpubl.

Conclusions

Center for Nutrition and Pregnancy

- We knew the placenta is defective by late pregnancy in embryos from ART (IVF, clones), which die at an extremely high rate – <10% survive to term, few survive after birth
- We showed that placental vascular development, and fetal and placental growth are compromised by ART very early in pregnancy
- Importantly, similar, if slightly less significant, defects occur during early pregnancy ET embryos
- We conclude that placental development, which supports fetal growth and development, is particularly sensitive to maternal 'stressors' during early pregnancy
- We have recently confirmed these observations in a model of maternal dietary restriction in a series of experiments in early pregnant cows*

NDSU NORTH DAKOTA STATE UNIVERSITY

*Crouse et al.,2017, 2019a,b; Greseth et al., 2017; McClean et al., 2017, 2018

The 'Problems of Pregnancy' Team

Center for Nutrition and Pregnancy

Internal (NDSU) Collaborators

Dr. Pawel Borowicz – Imaging and Microscopy, NDSU

Dr. Joel Caton – Animal Nutrition, NDSU

Dr. Carl Dahlen– Applied Animal Reproduction, NDSU

Dr. Anna Grazul-Bilska – Animal Embryology, NDSU

Dr. Steve O' Rourke – Vascular Pharmacology, NDSU

Dr. Dale Redmer – Animal Reproduction, NDSU

Dr. Reid Redden – Applied Animal Reproduction, NDSU (now Texas A&M)

Dr. **Chris Schauer** – Animal Nurtrion, NDSU

Dr. Kimberly Vonnahme – Animal Reproduction, NDSU (now Zoetis)

Dr. Alison Ward – Nutritional Epigenetics, NDSU

*** **Many former and current graduate and undergraduate students** ***

External Collaborators

Drs. Ryan Ashley – New Mexico State Univ.

Dr. Alan Conley – UC-Davis

Drs. Pilar Coy, Sebastian Canovas, Joaquin Gadea, Raquel Romar, Maria Jiminez-Movilla – University of Murcia, Spain

Dr. Kate Claycombe – Grand Forks Human Nutrition Research Center, USDA-ARS

Dr. Robert Cushman – U.S. Meat Animal Res. Center, USDA-ARS

Dr. Steve Ford – Univ. of Wyoming

Dr. Tom Geary - Fort Keogh Livestock & Range Res. Lab., USDA-ARS

Dr. Shireen Hafez – Virginia-Maryland Regional Coll. Vet. Med.

Dr. Caleb Lemley – Mississippi State Univ.

Dr. Lino Loi et al. – Univ. of Teramo, Italy

Dr. Allison Meyer – Univ. of Missouri

Dr. Kim Ominski et al. – Univ. of Manitoba

Drs. Brett Taylor & Greg Lewis – US Sheep **Res. Sta., Idaho**

Dr. Tom Spencer – University of Missouri

Dr. Jacqueline Wallace et al. – Rowett Inst., Univ. of Aberdeen, Scotland

Dr. Guoyao Wu et al. – Texas A&M Univ.

Funding

National Institutes of Health (NIH)

NHLBI NICHD

National Science Foundation
WHERE DISCOVERIES BEGIN

North Dakota INBRE

USDA United States Department of Agriculture
National Institute of Food and Agriculture
Agriculture and Food Research Initiative

EXP AGRICULTURAL EXPERIMENT STATION

Academic Scholarship

Society for Reproduction and Fertility

FULBRIGHT

FULBRIGHT España

NDSU NORTH DAKOTA STATE UNIVERSITY

Center for Nutrition and Pregnancy

"HEALTHY OFFSPRING THROUGH OPTIMAL NUTRITION"