The lung, the rain jacket and the not so bullet-proof vest: what can learn about placenta from sheep models of fetal development?

Martin G. Frasch, MD PhD

Dept. of Obstetrics and Gynecology
University of Washington, Seattle

http://fraschlab.org

UNIVERSITY of WASHINGTON

Conflict of interest

- Fetal EEG patent: US20110152633
- No further COI

HUMAN PLACENTA PROJECT

In a distant galaxy, long time ago …

- A scene in the delivery room:
- Physician/midwife: *Your baby is a girl! Would you like to hold her now?*
- Mother: *She is a miracle.*
- Physician/midwife: *One moment, push just a bit more…there… we delivered the placenta.*
- Mother: *Is that the afterbirth? May I see?*
- Physician/midwife: *Of course.*
- Mother: *Oh, that's gross. What do you do with that now?*
- Physician/midwife: *Well, we commonly throw it away. It is a biohazard you know?*

How the placenta affects your life, from womb to tomb
D. M. Nelson, *AJOG*,
213(4), Suppl., Pages S12–S13; doi:10.1016/j.ajog.2015.08.015

NEWS RELEASES

Thursday, February 26, 2015

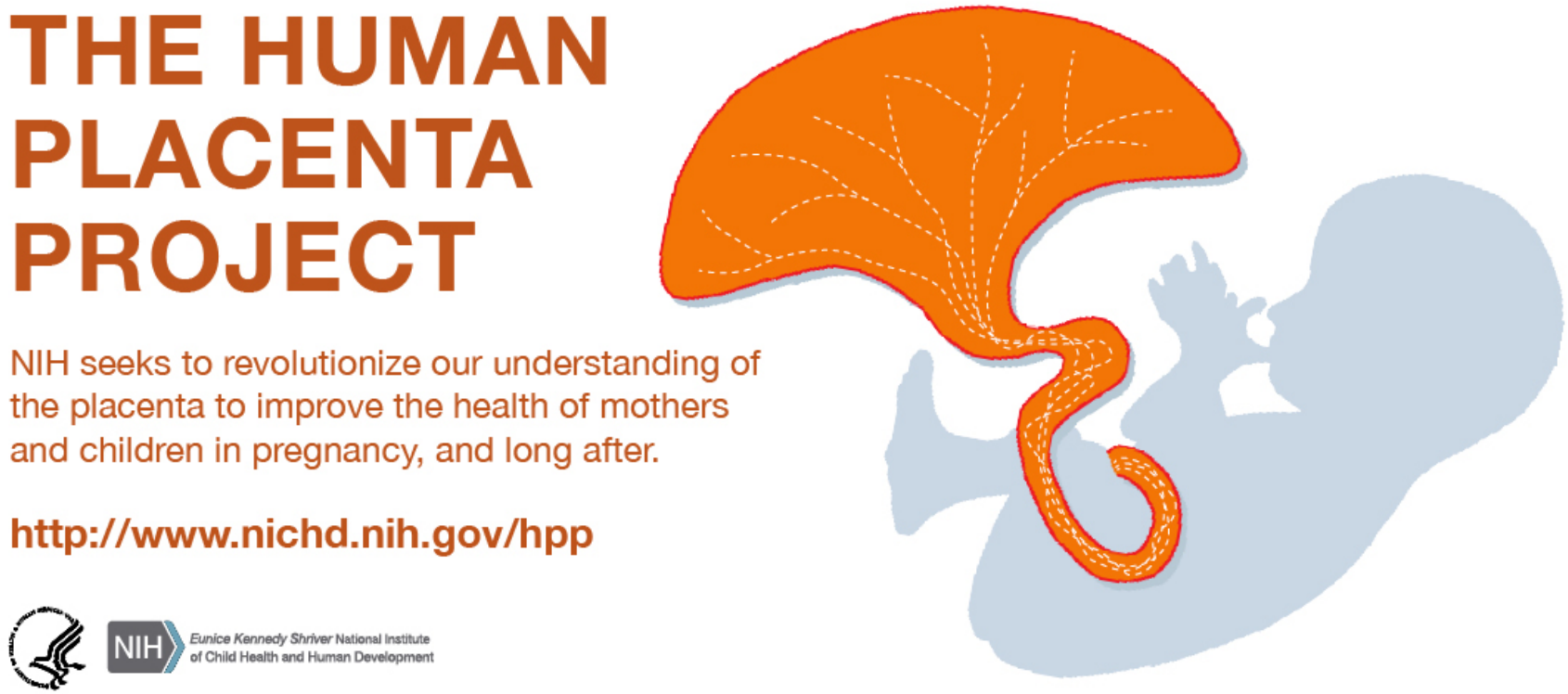
NIH announces $41.5 million in funding for the Human Placenta Project

Better understanding of the placenta promises to improve the health of mothers and children.

Institute/Center

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

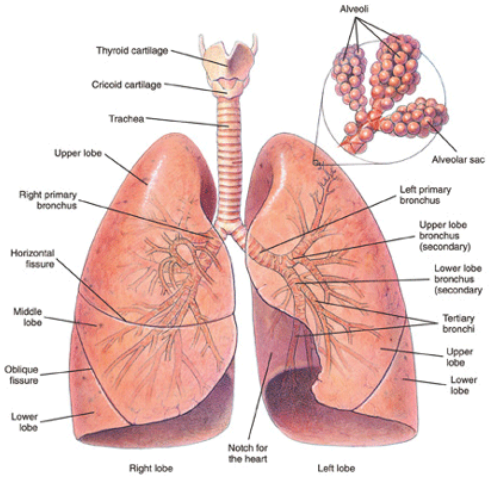
National Institute of Biomedical Imaging and Bioengineering (NIBIB)



Biohazard becomes central stage actor: from womb to tomb

Stress
Diet
Hypoxia
Infections
Environment

Labour



PTB

DoHAD

Clinical motivation

- Diagnostic potential to relate to other organ injuries:
  - MR
  - placenta-derived biomarkers (alarmins)
  - Exosome signalling
  - role as mediator of maternal stress via pCRH onto fetal development and placental clock

- Acute impact: chronic and acute hypoxia, labour
- Long-term impact: DoHAD

- Need different animal models to study different functions

- Focus on fetal sheep model

Reynolds et al, Placenta 2005, 26, 698-708

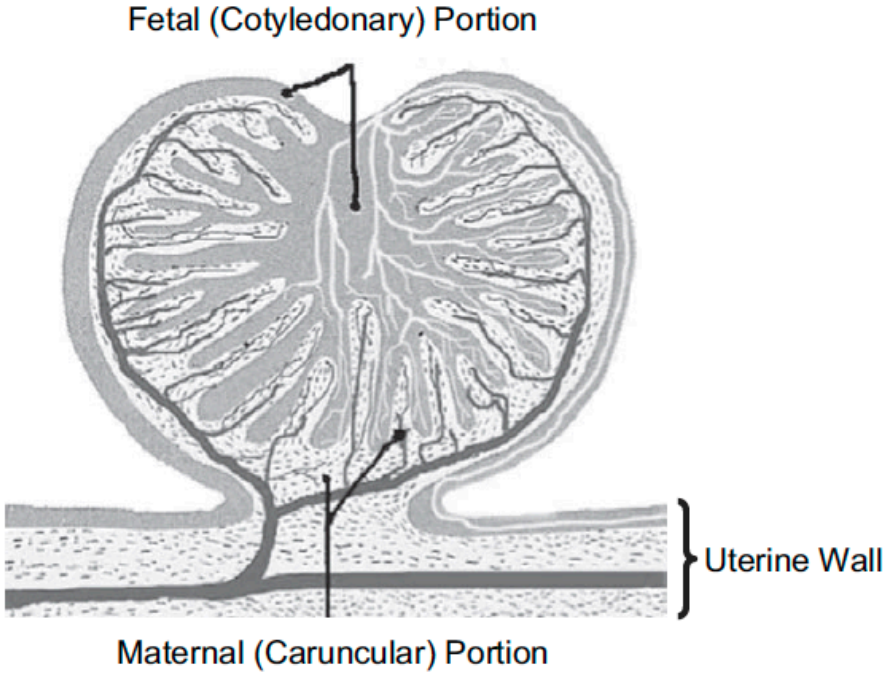
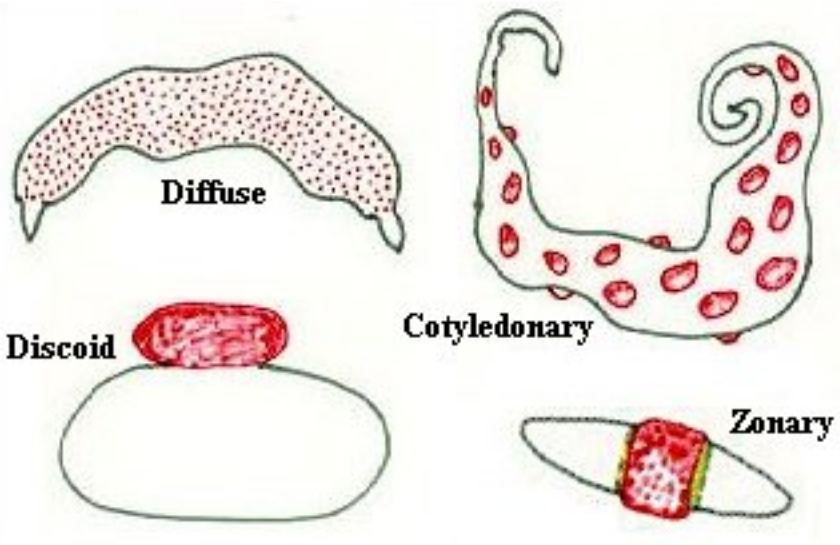
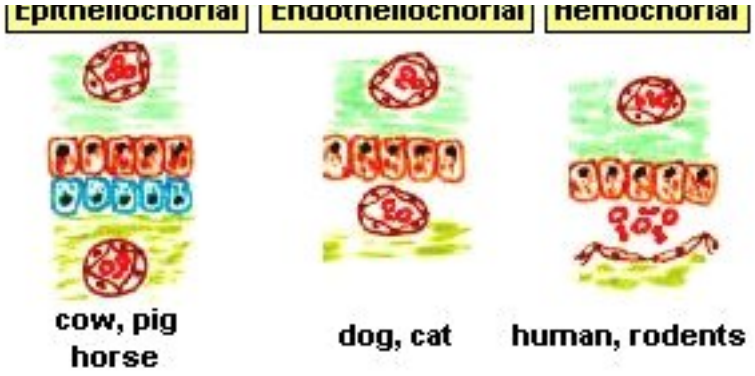


Figure 1. Schematic representation of the sheep placentome. The stippled areas represent the maternal, or caruncular, portion, and the grayish areas represent the fetal, or cotyledonary, portion. The vascular supply for each portion of the placentome is represented by the dark grey (maternal, caruncular) or whitish (fetal, cotyledonary) vessels. Figure adapted from Ramsey [9].

Human	Sheep
discoid	cotyledonary
endotheliochoreal	epitheliochoreal





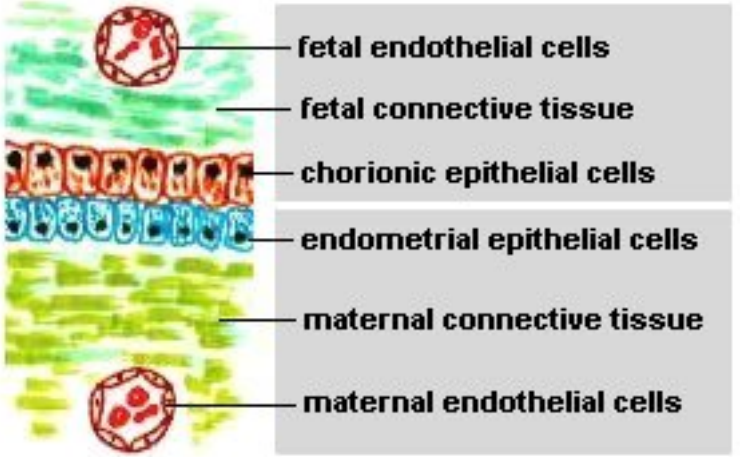
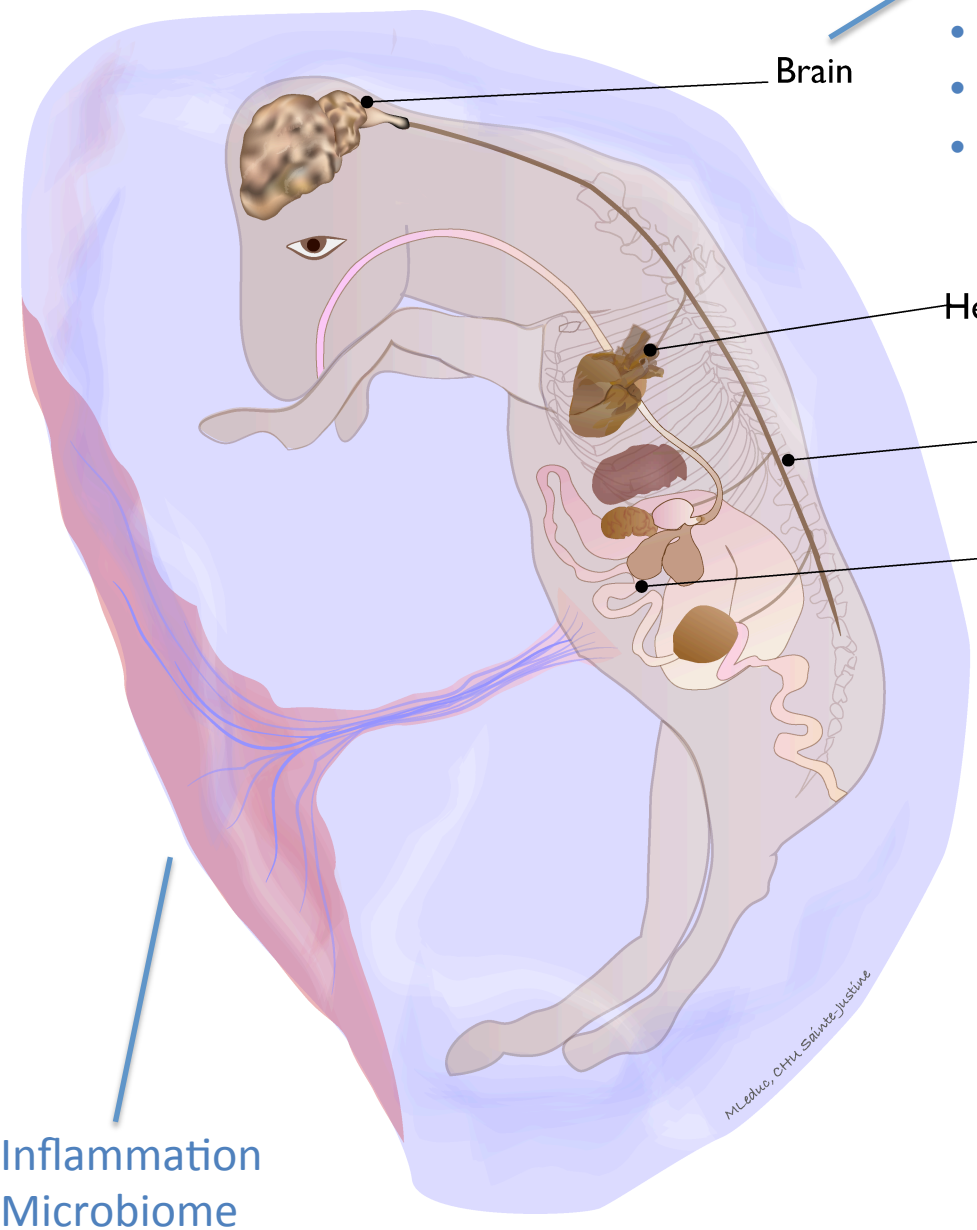


Table 1. Placental types in superorders and orders

Placenta type	Superorder	Order
Haemochorial	Laurasiatheria	Carnivora—hyaenas only
		Chiroptera—many bat families
		Insectivora—hedgehogs
	Euarchontoglires	Rodentia—most families
		Lagomorpha—rabbits, pikas
		Primata—monkeys, gorillas, man, Tarsius
		Dermoptera—flying lemurs
	Xenarthra	Xenarthra—armadillos, anteaters
	Afrotheria	Hyracoidea—hyraxes, conies
		Afrosoricida—tenrecs, golden moles
		Macroscelidea—elephant shrews
Endotheliochorial	Laurasiatheria	Carnivora—all but hyaena
		Pinnipedia—seals, walruses
		Chiroptera—several bat families
		Insectivora—shrews
	Euarchontoglires	Rodentia—kangaroo rat
		Scandentia—tree shrews
	Xenarthra	Xenarthra—sloths
	Afrotheria	Proboscidea—elephants
		Tubulidentata—aardvark
		Sirenia—manatee
Epitheliochorial	Laurasiatheria	Cetacea—whales, porpoises
		Artiodactyla—cows, pigs, deer
		Perissodactyla—horses, tapirs
		Pholidota—pangolin
	Euarchontoglires	Primata—lemurs, lorises

Enders & Carter, Placenta 2004, 25, Suppl. A, (18) S3-S9



- EEG
- Blood flow
- MRI
- HRV
- Inflammation *in situ* and *in vitro*

- ECG
- HRV

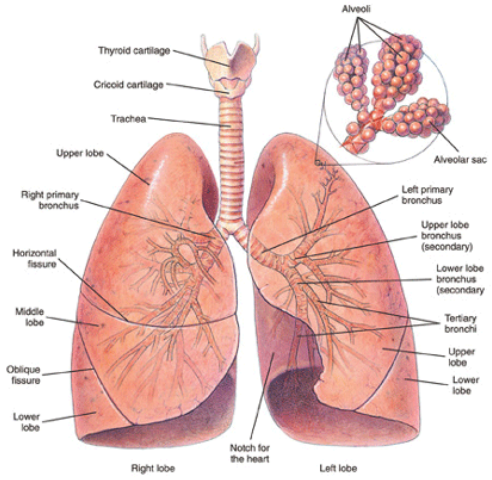
- HRV
- Vx or VNS

- Blood flow
- HRV
- Inflammation *in situ*
- Microbiome

- Inflammation
- Microbiome

Fetal sheep models where placenta matters

Labour



Hypoxia
Infections

PTB

Stress
Diet

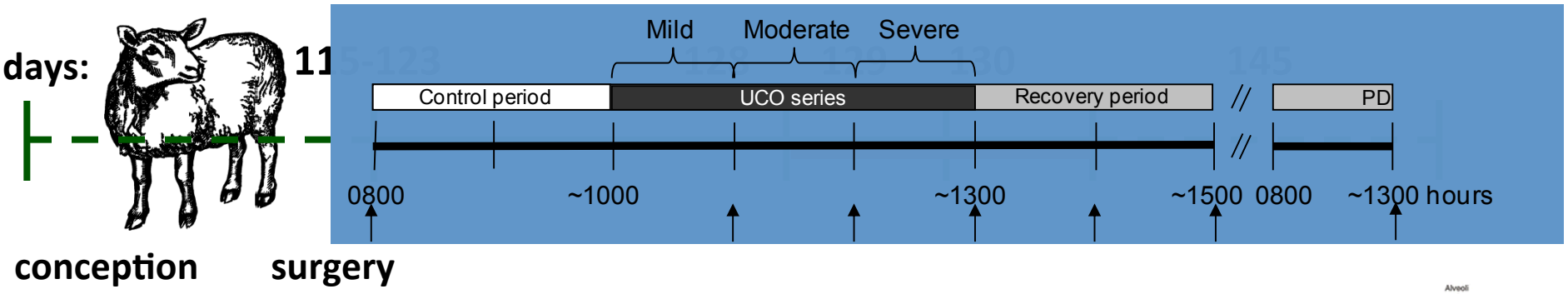
Infections
Environment

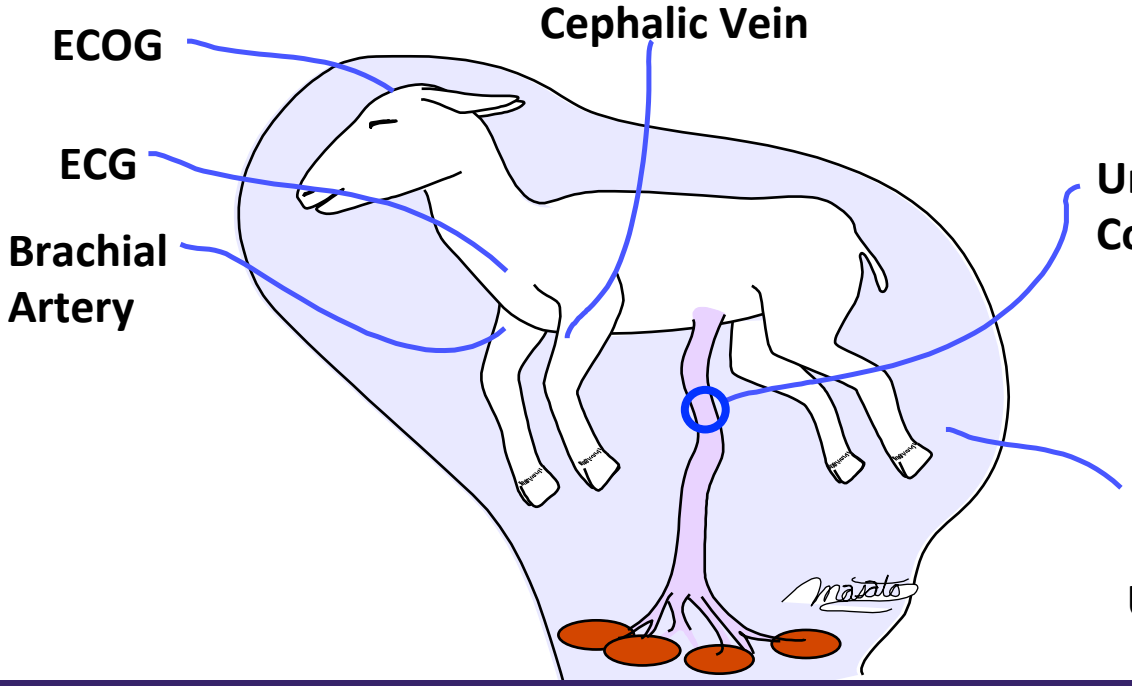
DoHAD

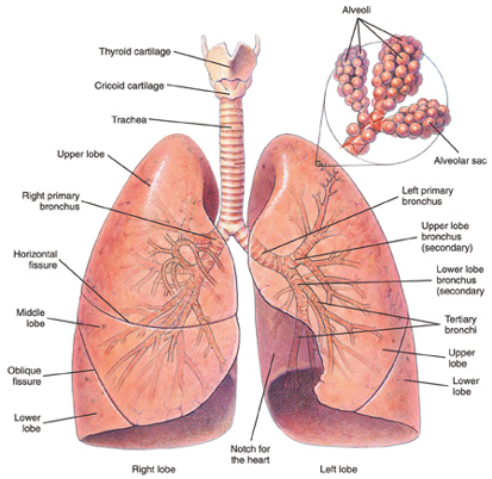
Stress
Diet
Hypoxia
Infections
Environment

Experimental design: acidemia

gestational age: 0.76-0.84 **0.89 (human week 35)**



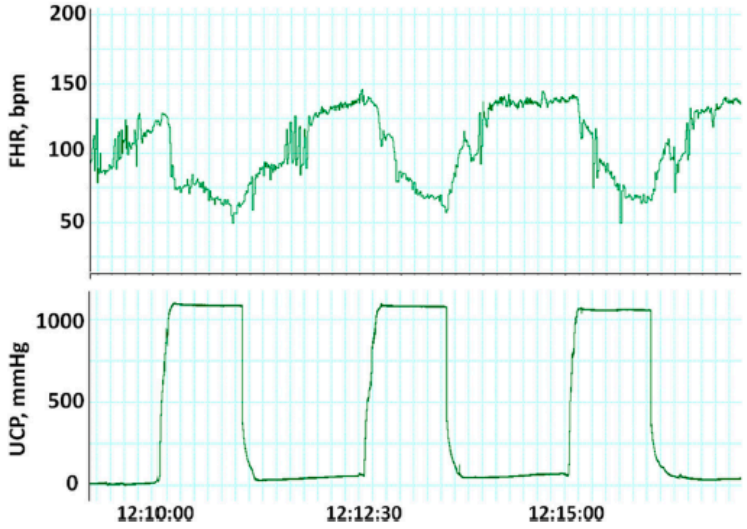




UCO, Umbilical Cord Occlusion

Labour

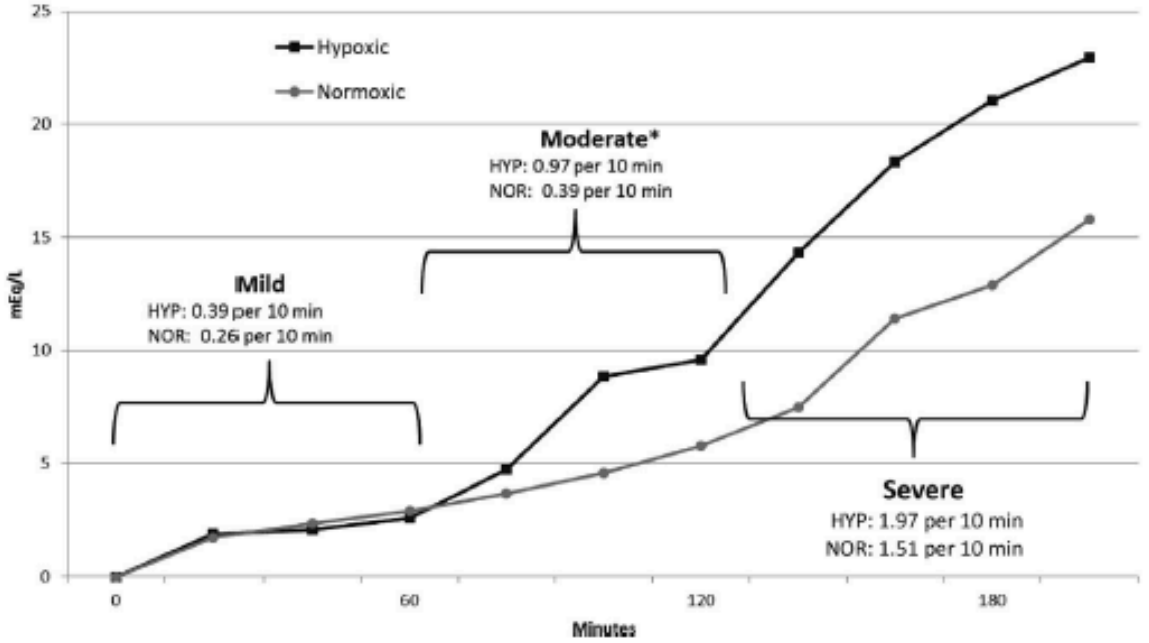
FIGURE 2
FHR deceleration pattern



Representative fetal heart rate (FHR) with associated umbilical cord occlusion (UCO). UCO is measured by umbilical cord pressure (UCP) in mm Hg.

Amaya et al. Accelerated acidosis in response to variable fetal heart rate decelerations in chronically hypoxic ovine fetuses. Am J Obstet Gynecol 2016.

FIGURE 7
Fetal base deficit change



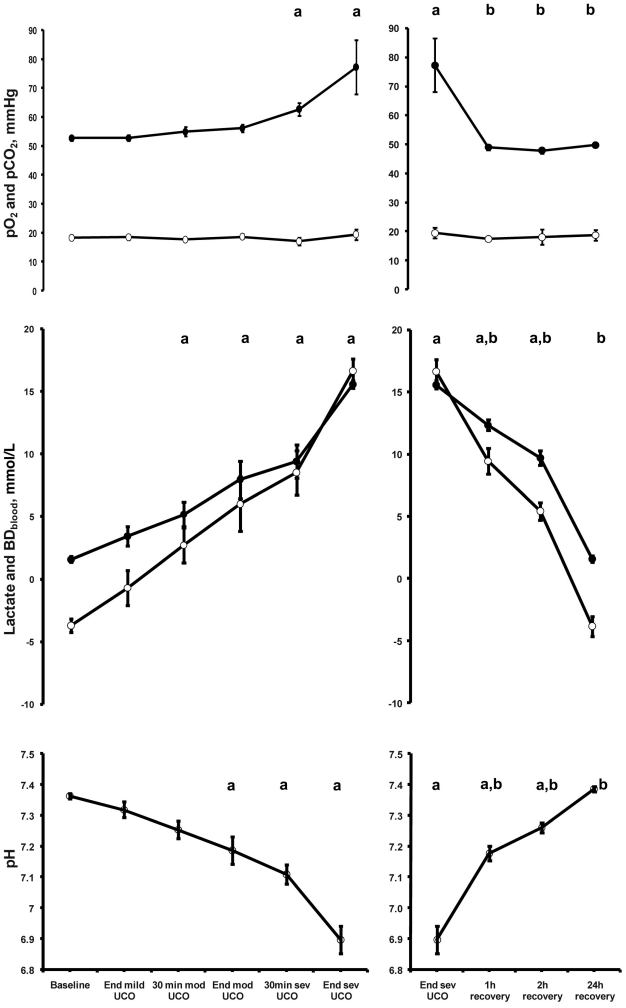
Fetal base deficit change during mild, moderate, and severe variable decelerations. *$P < .05$.

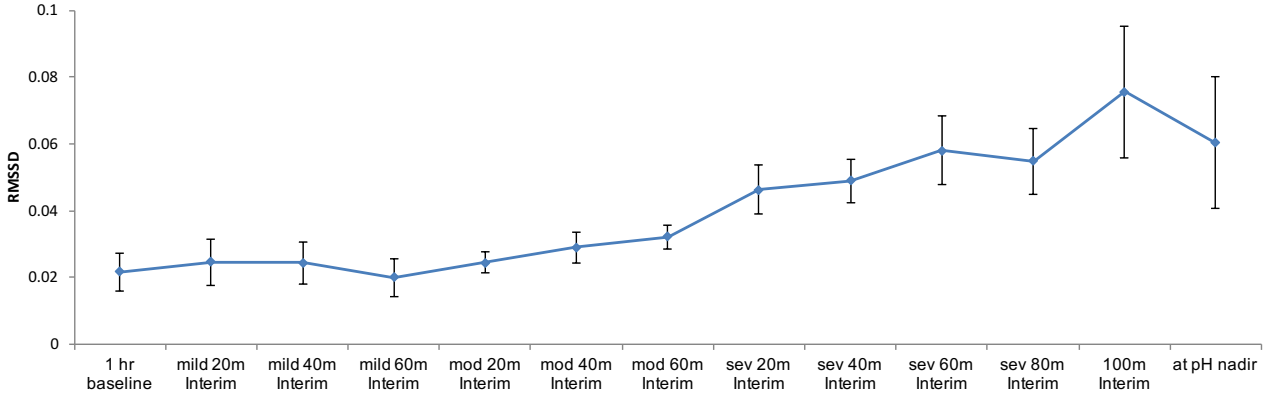
HYP, hypoxic; *NOR*, normoxic.

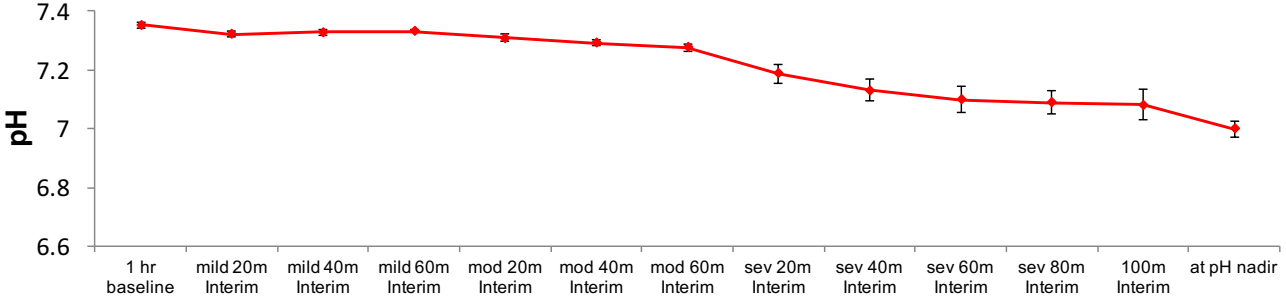
Amaya et al. Accelerated acidosis in response to variable fetal heart rate decelerations in chronically hypoxic ovine fetuses. Am J Obstet Gynecol 2016.

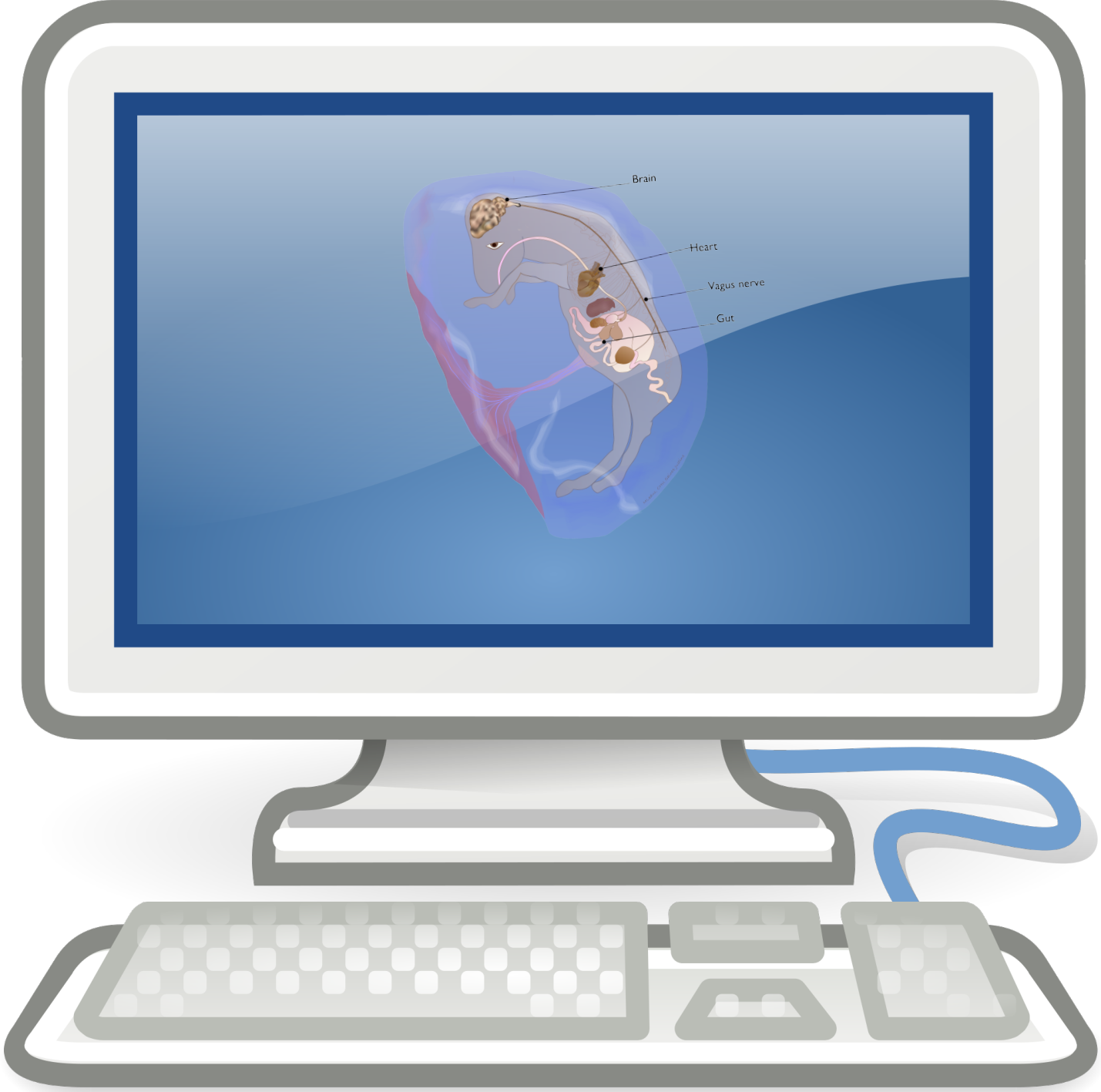
What can we see non-invasively?

- Placental CO_2 clearance and anaerobic metabolism with lactic acid accumulation can be monitored non-invasively using fetal heart rate

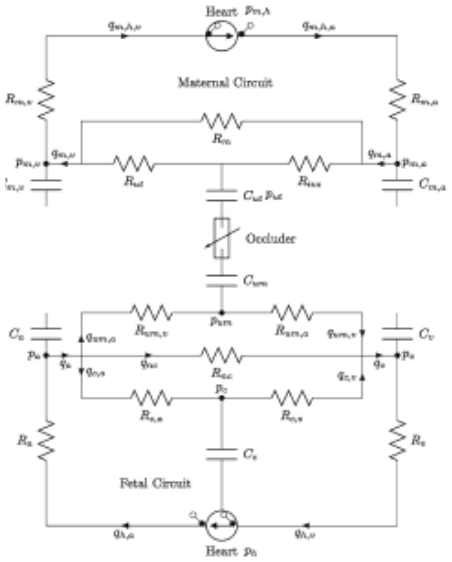


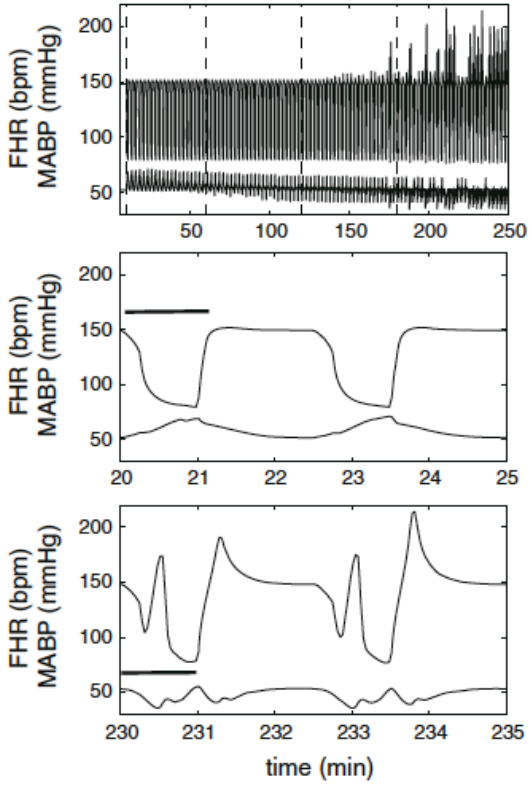


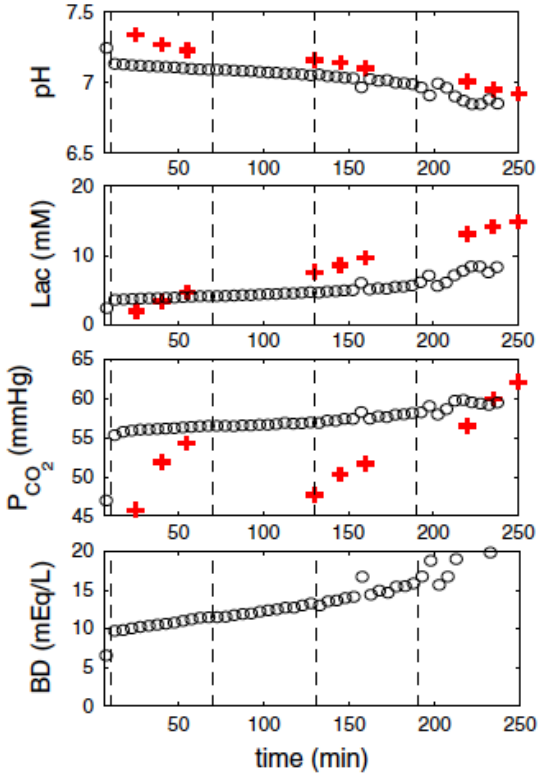


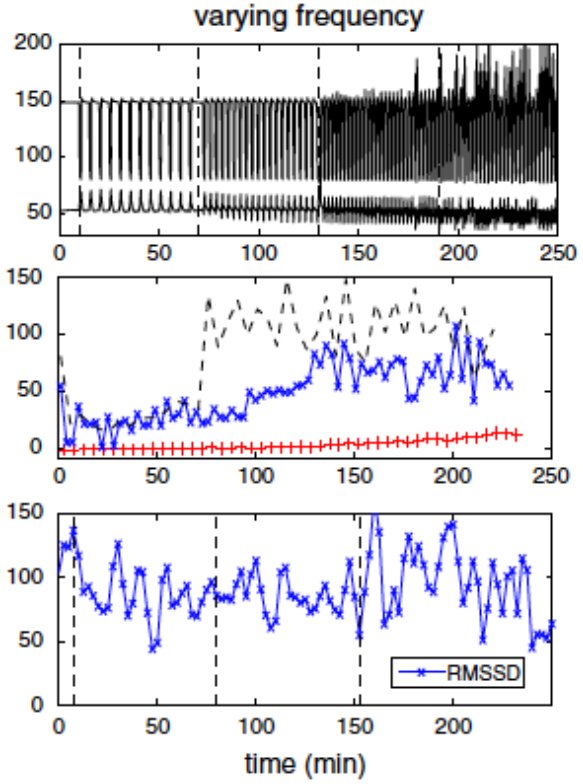

Brain
Heart
Vagus nerve
Gut

In silico labour model: insights into placental function

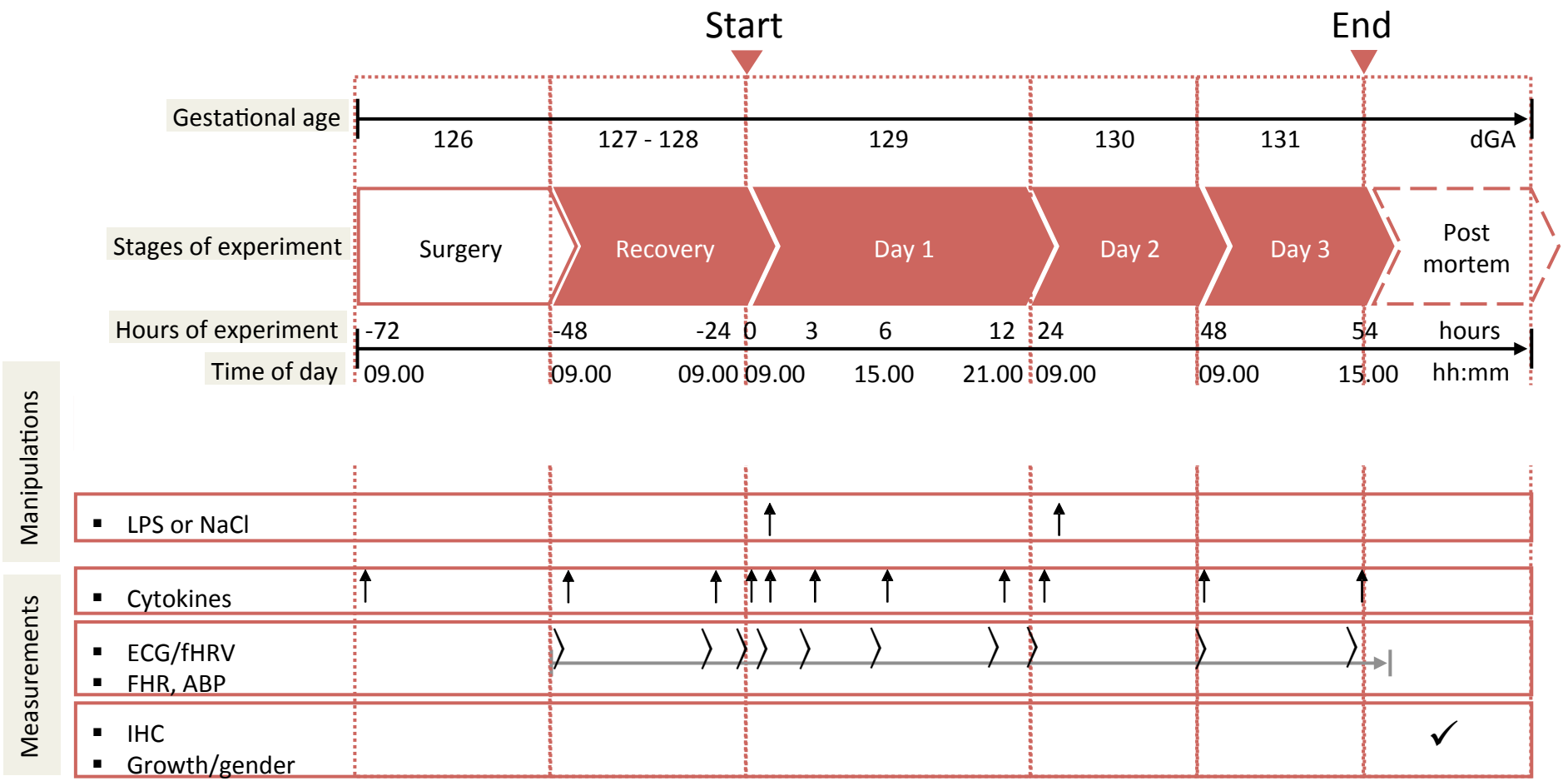




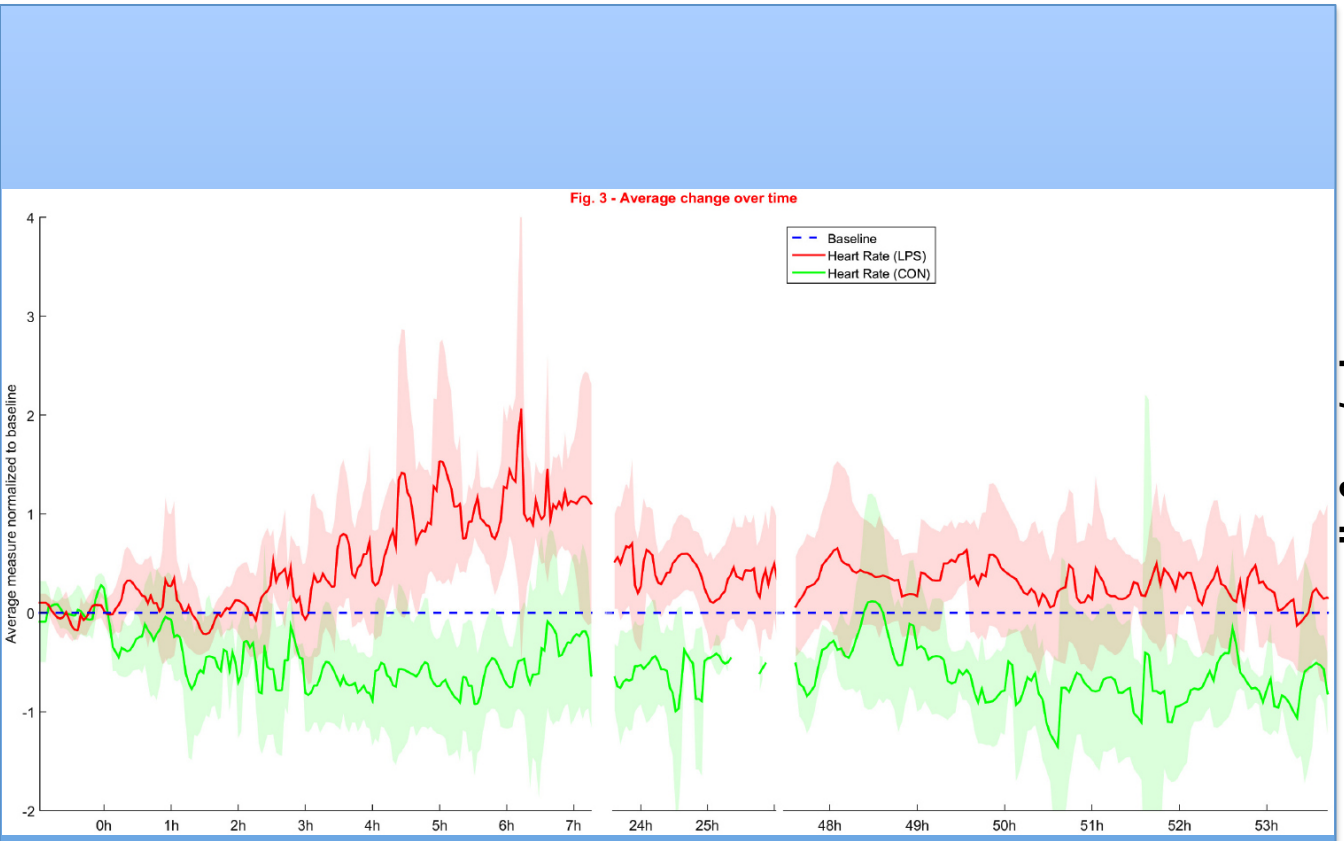




Experimental design: inflammation



Fetal HRV inflammation signature



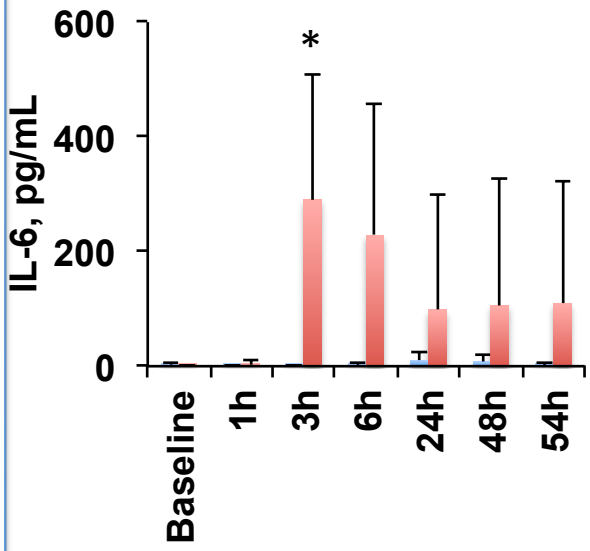


Figure 3 from Does heart rate variability reflect the systemic inflammatory response in a fetal sheep model of lipopolysaccharide-induced sepsis?
Lucien D Durosier et al 2015 Physiol. Meas. 36 2089 doi:10.1088/0967-3334/36/10/2089

Original Article

A Cross-Species Analysis of Animal Models for the Investigation of Preterm Birth Mechanisms

Brian W. Nielsen, MD, MS[1], Elizabeth A. Bonney, MD, MPH[1], Bradley D. Pearce, PhD[2], Leah Rae Donahue, PhD[3], and Indra Neil Sarkar, PhD, MLIS[4]; for the Preterm Birth International Collaborative (PREBIC)

Reproductive Sciences
1-10

DOI: 10.1177/1933719115604729
rs.sagepub.com
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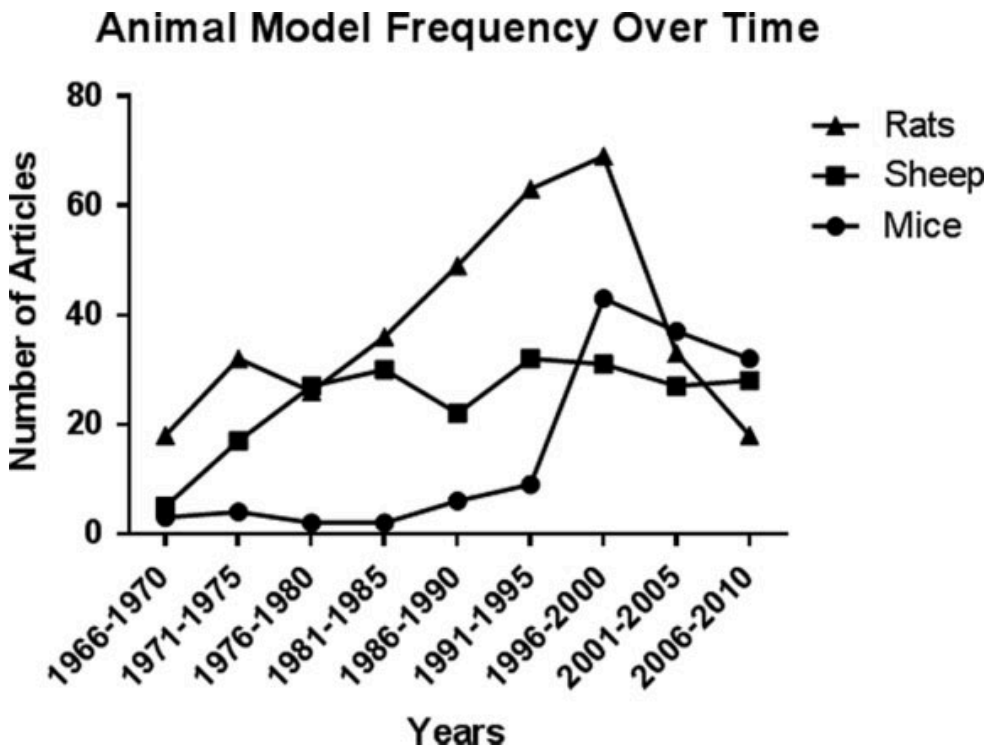
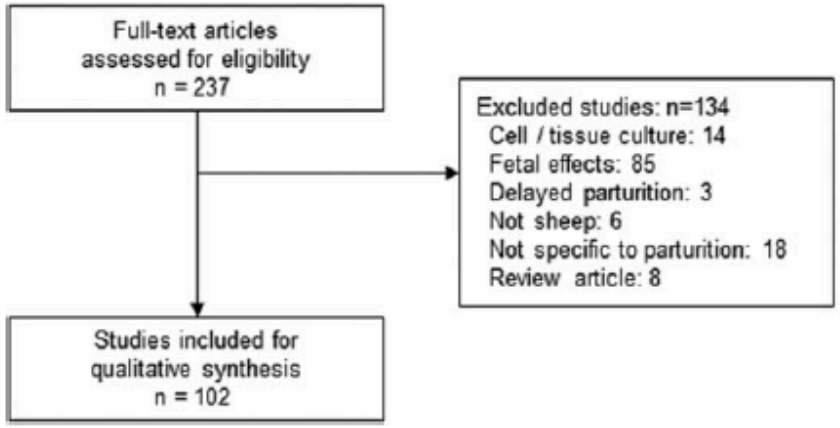


Studies according to animal species n=	
Rats: 352	Guinea Pigs: 32
Sheep: 237	Goats: 20
Cattle: 201	Hamsters: 15
Mice: 150	Cats: 7
Swine: 131	Lizards: 5
Rabbits: 76	Marsupialia: 4
Non-Human Primates: 66	Camelids, New World: 2
Horses: 59	Deer: 2
Dogs: 32	Opossums: 1

Figure 4. Animal models literature organized by species (n).



Author	Year	Reference	Induction Method
Masaoka N	2011	[24]	Lipopolysaccharide
Young IR	1996	[21]	PGE_2
Schlafer DH	1994	[23]	Salmonella
Taylor MJ	1982	[22]	Epostane (Anti-progestin)
Harman EL	1980	[20]	PGF_{2a} and Flumethasone
Cahill LP	1976	[18]	Estradiol
Liggins GC	1969	[17]	Glucocorticoids
Liggins GC	1968	[16]	ACTH or Cortisol

Figure 6. Sheep models of preterm birth. Review of full-text articles within the sheep Medical Subject Headings (MeSH) descriptor. Classifi-

Placental programming of chronic diseases, cancer and lifespan: A review

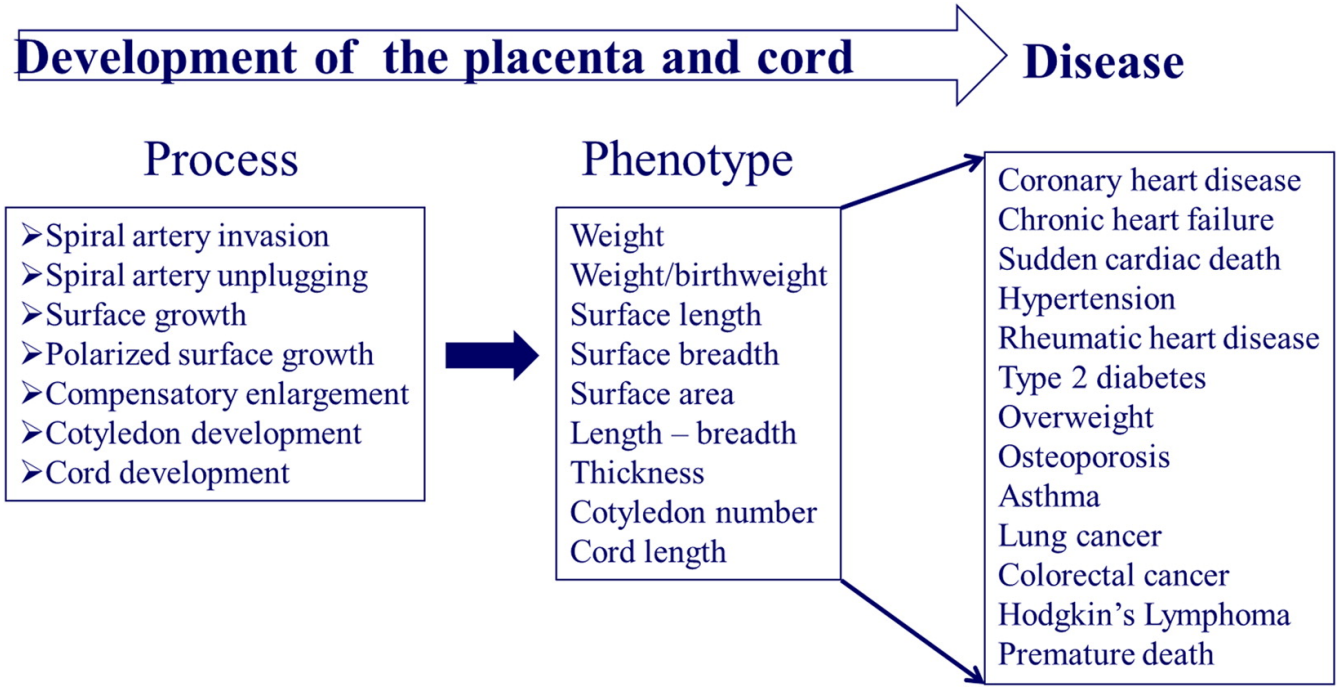
D.J.P. Barker, K.L. Thornburg

Placenta
Volume 34, Issue 10, Pages 841-845 (October 2013)
DOI: 10.1016/j.placenta.2013.07.063

VIEWPOINT ajog.org

The placenta is the center of the chronic disease universe

Kent L. Thornburg, PhD; Nicole Marshall, MD



Placenta 2013 34, 841-845DOI: (10.1016/j.placenta.2013.07.063)

TABLE

Coronary heart disease in men born to tall mothers (>160 cm) according to her body mass index

Variable	Mother's BMI ≤26 kg/m^2 HR (95% CI)	Mother's BMI >26 kg/m^2 HR (95% CI)
Placental weight, g		
≤550	0.8 (0.4–1.3)	2.2 (1.3–4.0)
–650	0.9 (0.6–1.5)	1.9 (1.2–3.2)
–750	0.8 (0.5–1.4)	1.0 (baseline)
P value for trend	.5	.002
Placental area, cm^2		
≤225	1.0 (0.6–1.7)	2.2 (1.4–3.7)
–255	1.0 (0.6–1.6)	1.3 (0.8–2.2)
–295	1.1 (0.7–1.9)	1.7 (1.0–.7)
>295	1.0 (baseline)	1.0 (baseline)
P value for trend	.5	< .001

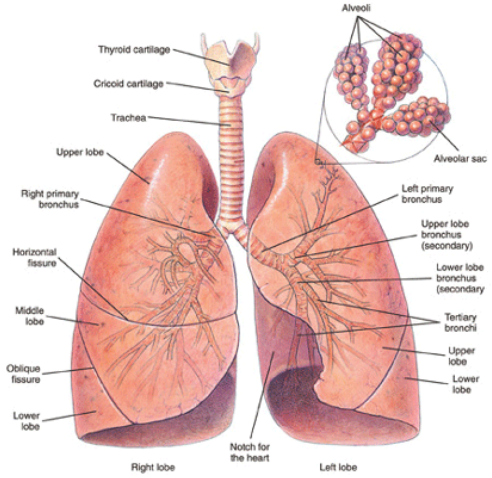
The table shows that risks for acquiring coronary heart disease in men depends on maternal stature and body mass index. Among men born in Helsinki to taller mothers with a high body mass index, low placental weight and surface area were associated with coronary heart disease.[72]

BMI, body mass index. *CI*, confidence interval; *HR*, hazard ratio.

Thornburg. The placental roots of chronic disease. Am J Obstet Gynecol 2015.

Prime time for sheep placenta project?

Labour



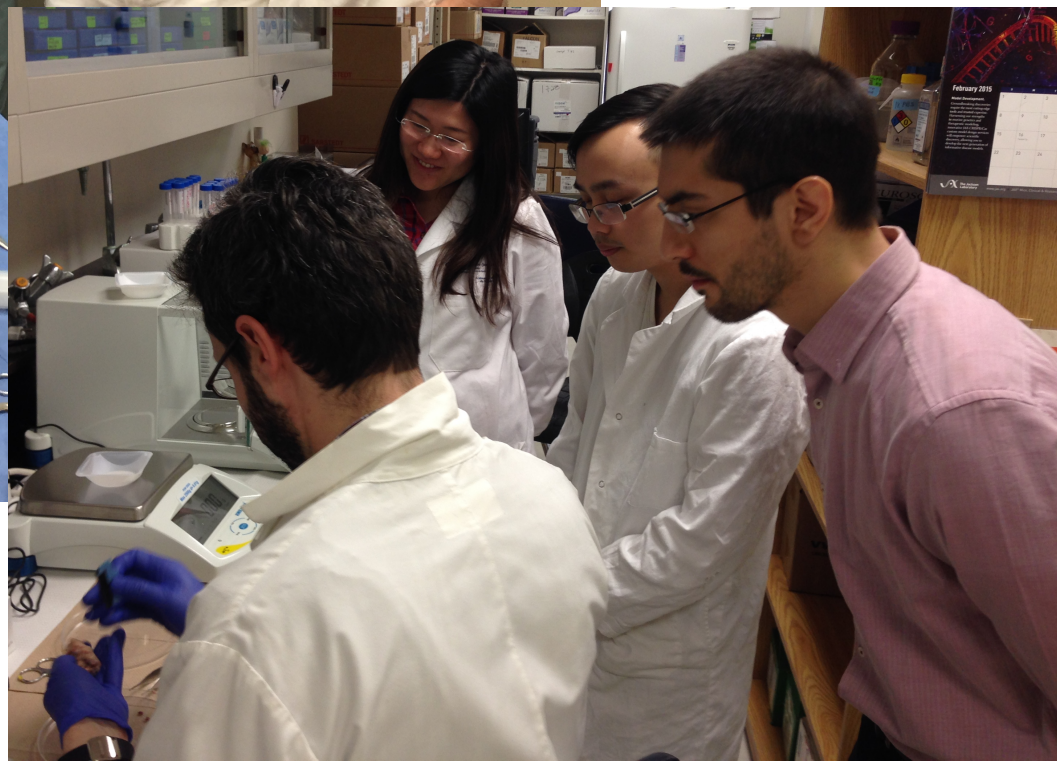
PTB

DoHAD

Acknowledgements

Faculté medicine veterinaire team,
Université de Montréal
Bryan Richardson lab, *Western University*, London, ON
Michael Ross, *UCLA*
Andrew Seely lab, *Ottawa University*, ON
Enrico Ferrazzi team, *University of Milan,* Italy
Dept. of Math/Stat team, *York University*, ON

Funding:
Molly Towell Perinatal Research Foundation
CIHR, FRSQ
QTNPR (CIHR)
NeuroDevNet


February 2015