Impact of Environmental Perturbations on Placental Perfusion and Function

Jamie Lo MD MCR, Associate Professor
Maternal Fetal Medicine
Oregon Health & Science University
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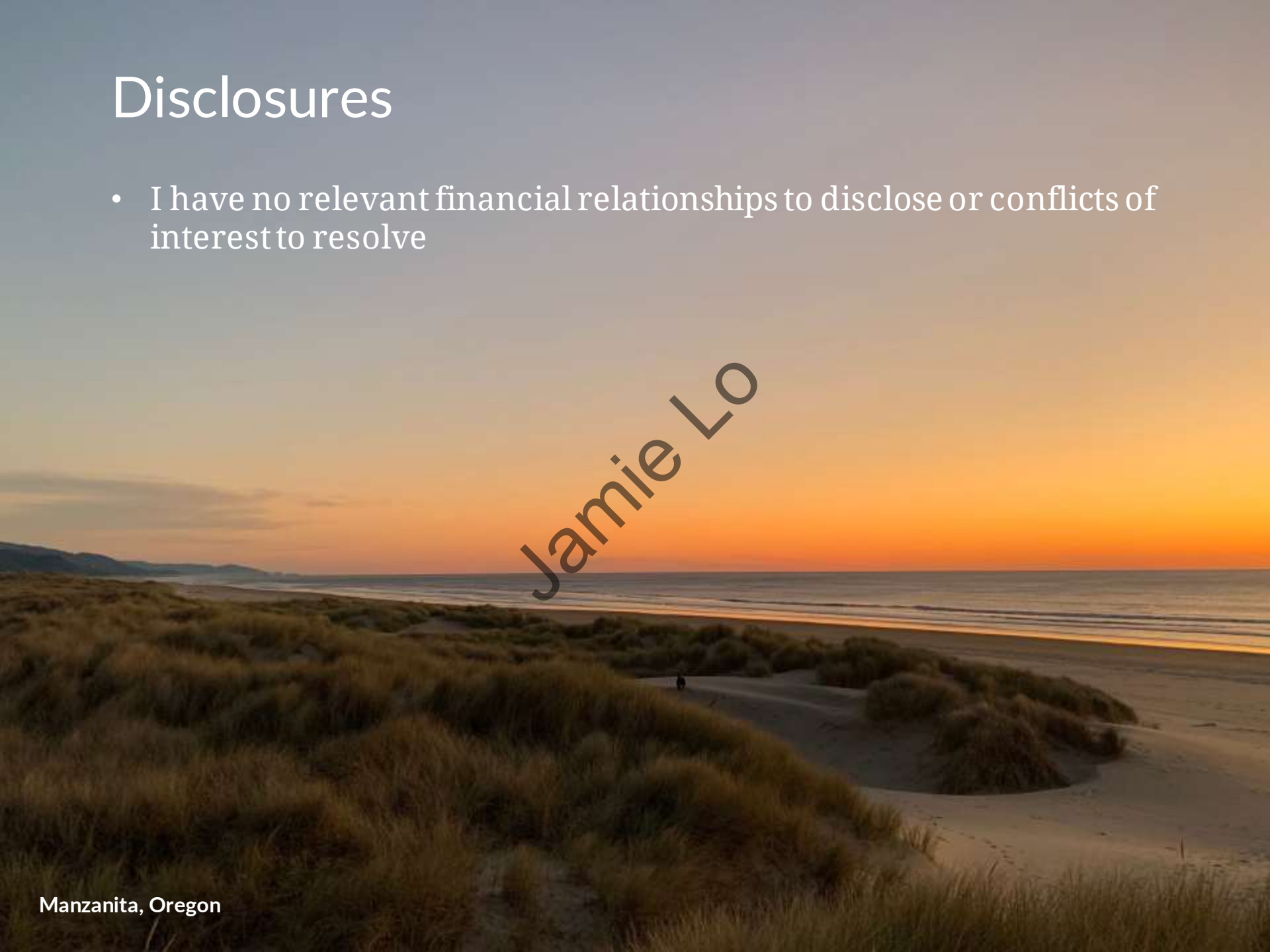
Disclosures

- I have no relevant financial relationships to disclose or conflicts of interest to resolve



Manzanita, Oregon

Prenatal Origins of Health and Disease

Altered maternal environment during pregnancy can influence fetal development and predispose to diseases later in life

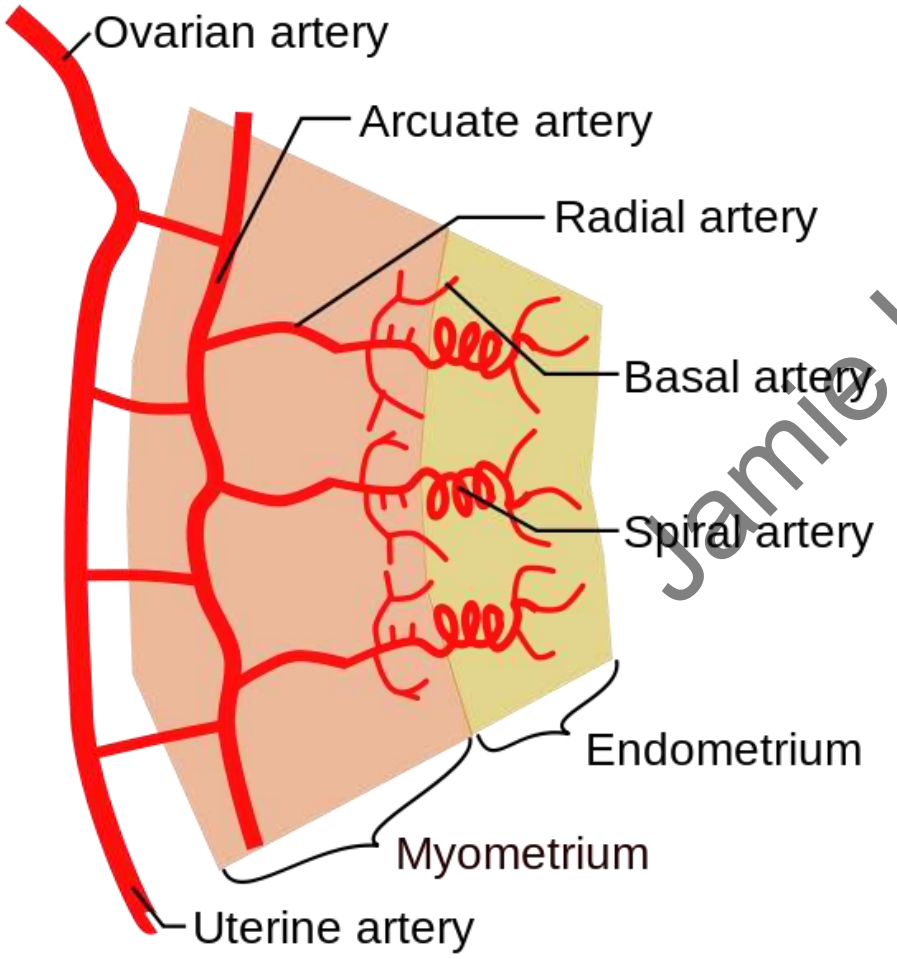
- Hypoxia
- Stress
- Obesity
- Diabetes
- Toxins
- Altered nutrition
- Inflammation
- Reduced utero-placental blood flow

Placental Plasticity and Adaptation

- Placental plasticity is the ability of the placenta to adapt and alter its growth trajectory in response to altered fetal requirements.
- Placental dysfunction, including structural or perfusion abnormalities, has been shown to result in increased fetal morbidity or mortality
- Limits of placental plasticity remains poorly understood

References: *Dimasuay K, et al. 2016; Roberts V et al. 2013*

Placental structure: Maternal



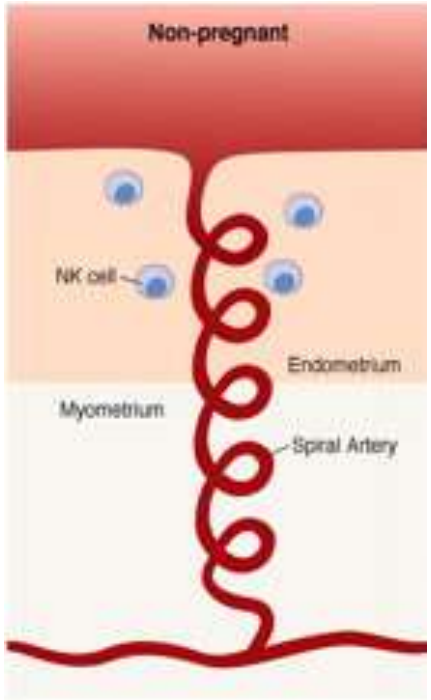
Non-pregnant: spiral arteries supply blood to the endometrium during luteal phase of the menstrual cycle

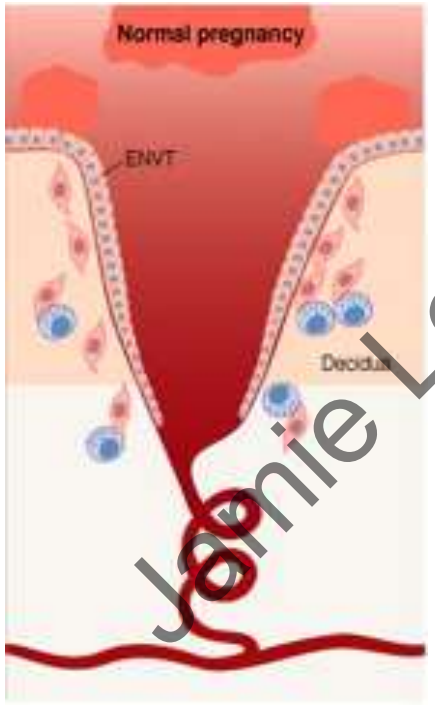
Pregnancy: spiral arteries transformed for utero-placental flow

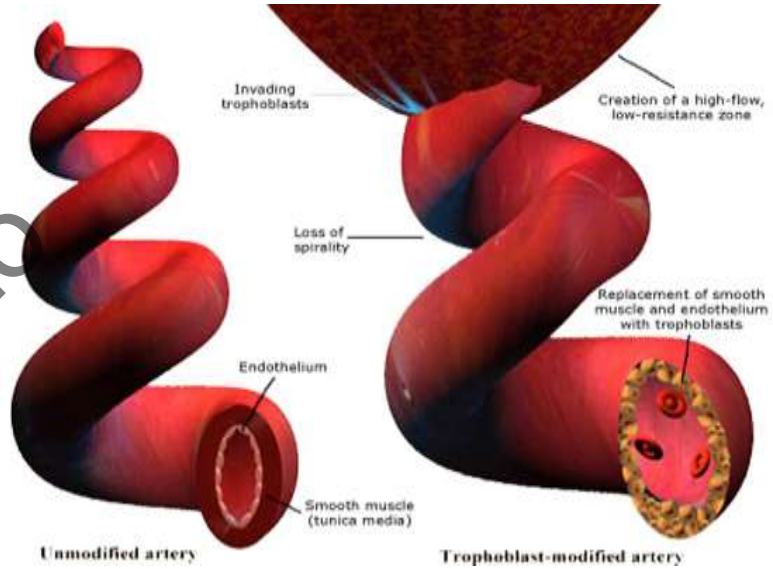
Non-pregnant: endometrial decidualization conducive to pregnancy

Pregnancy: endometrium-> decidua

Placental structure: Maternal





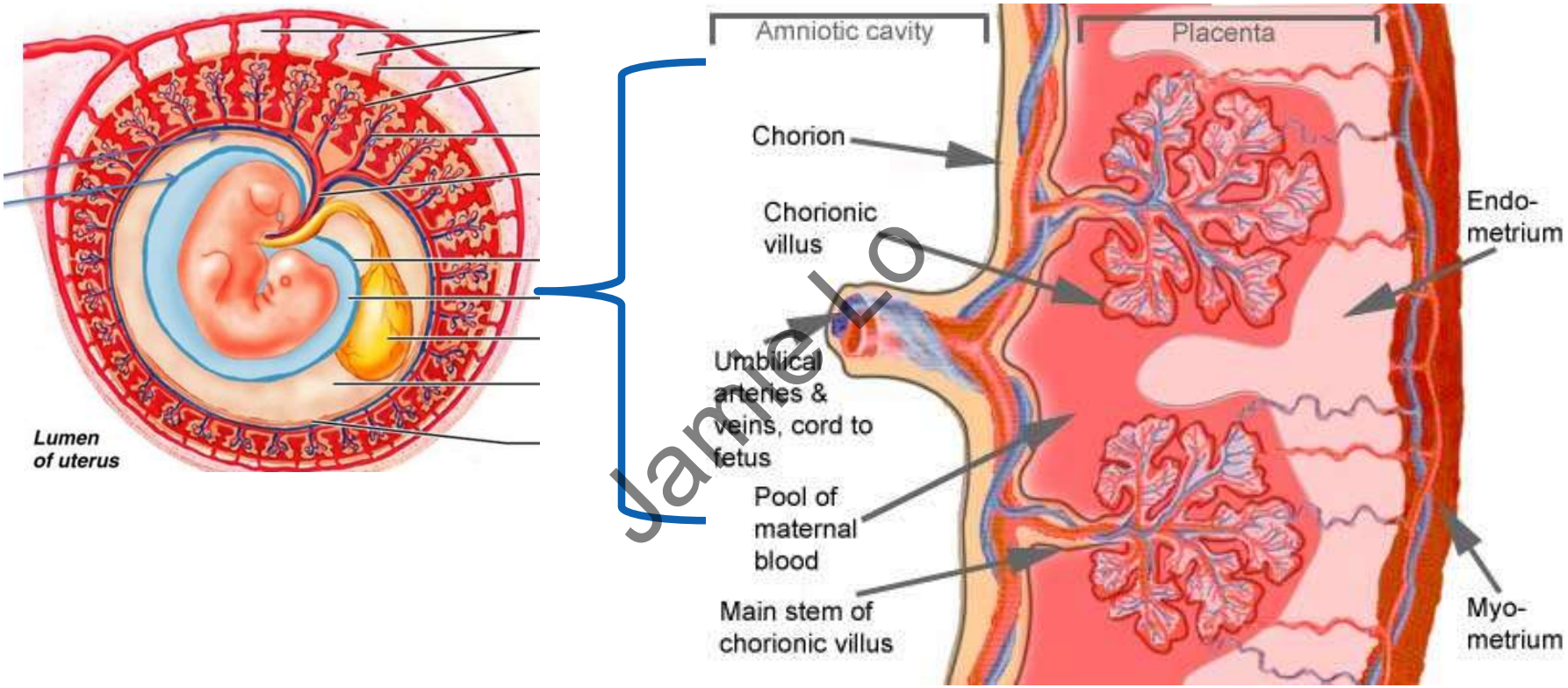


Trophoblast cells invade spiral arteries in the ***decidua basalis*** layer

Normal: invasion to just *beyond* the decidua-myometrial border

Normal: loss of vascular smooth muscle causes the vessel to *dilate*

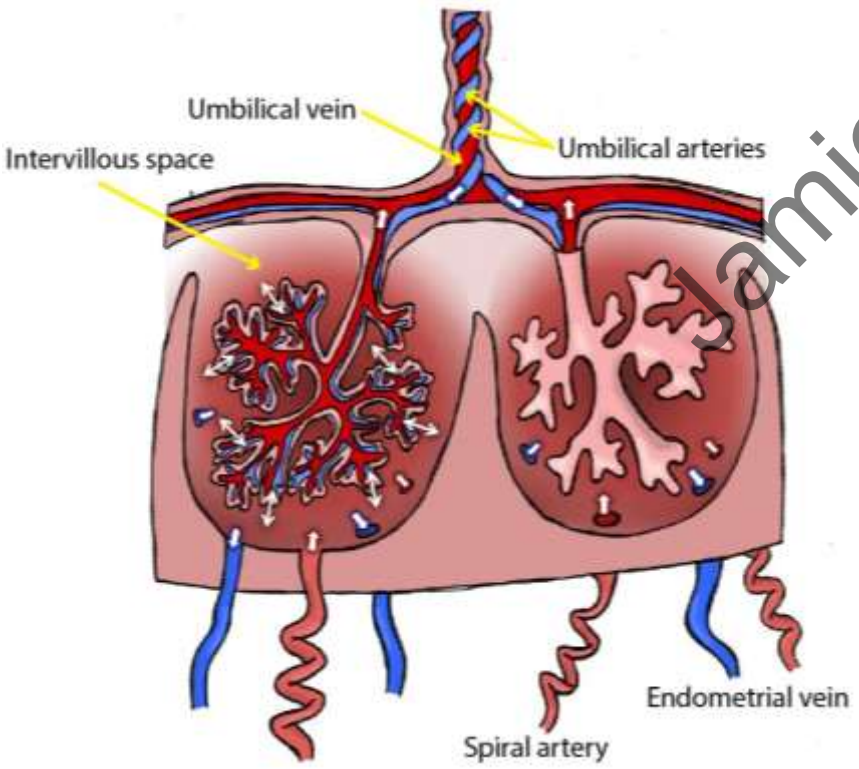
Placental structure: Fetal



Fetal umbilical arteries and umbilical vein branch into ***capillary beds*** that fill the intervillous space within the chorionic plate

Limitations to Existing Human Studies

- Human data is heterogenous and confounded
- There is no comprehensive tool to adequately assess placental function and perfusion non-invasively



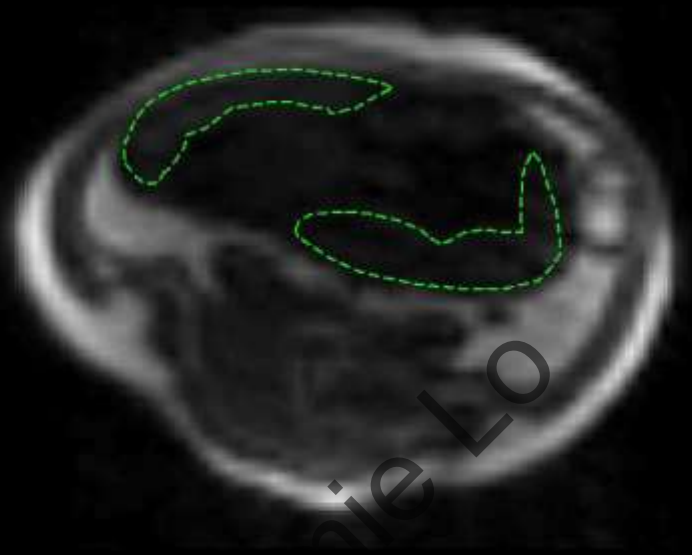
Doppler Ultrasound

References: Schabel et al. MRM (2016)

Translational models

- Permit necessary experiments not feasible or ethical in humans
- Allow examination of specific environmental insults
- Minimize confounders and inter-individual variability
- Non-human primate has a similar hemochorial placental structure and developmental ontogeny

Dynamic Contrast-Enhanced MRI (DCE-MRI)

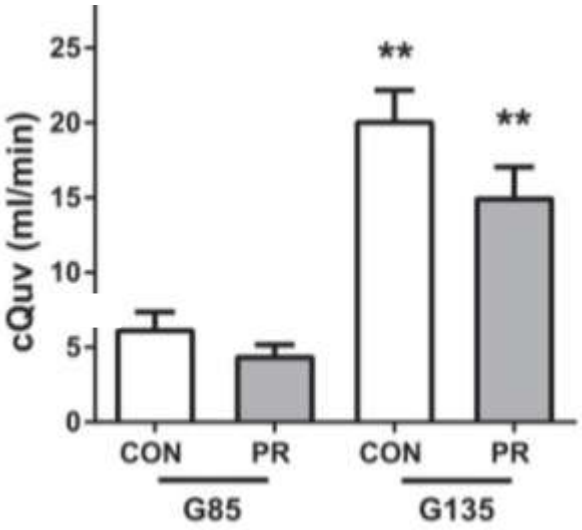


- Contrast agent in maternal circulation
- Non-invasive imaging method that can evaluate blood flow in the entire placental unit simultaneously
  - Can measure comprehensive blood flow and intervillous volume
  - Allows quantification of regional placental blood flow differences

Impact of Maternal Protein Restriction

- Maternal malnutrition impacts fetal growth
- In underdeveloped countries, malnutrition typically takes the form of poor dietary protein intake
- Non-human primate model of gestational protein restriction
  - Control diet (CON, 26% protein)
  - Protein restriction diet (PR, 13% protein)
- 50% reduction in dietary protein results in reduced placental perfusion, fetal growth restriction, a 50% rate of pregnancy loss, and reduced total protein of amniotic fluid

Placental volume blood flow

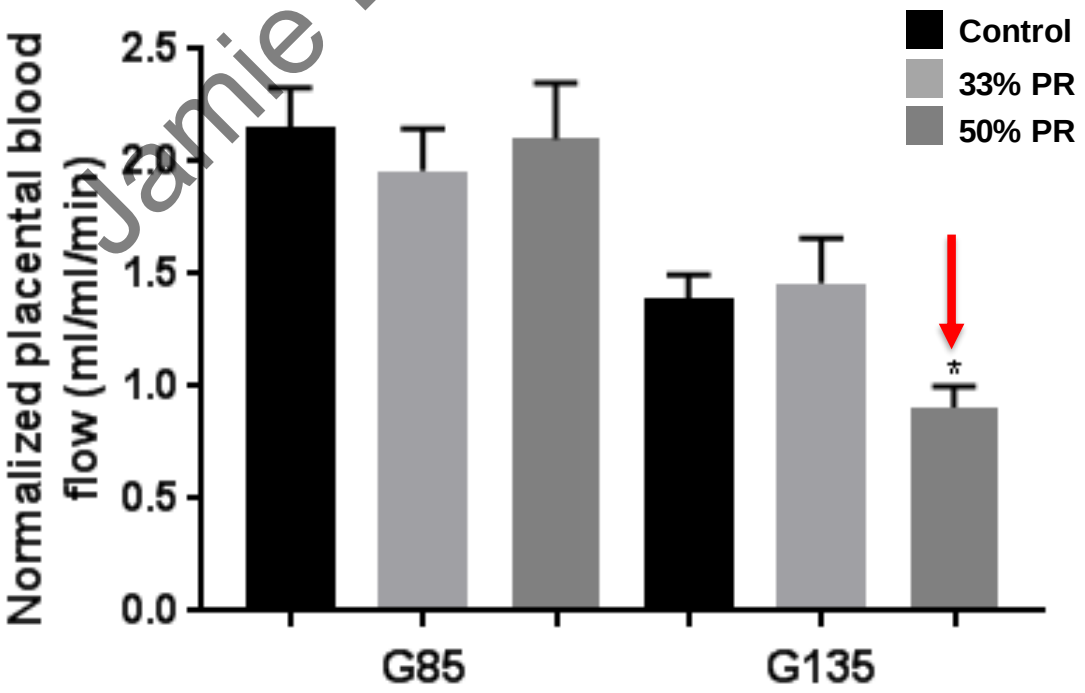


References: *Roberts V, et al. 2018*

Impact of Maternal Protein Restriction

- Control diet (CON, 26% protein)
- Protein restriction (PR)
  - 33% PR (17% protein)
  - 50% PR (13% protein)

Pregnancy Loss	
Control	0/8
33% PR	1/8
50% PR	3/8



*p<0.05

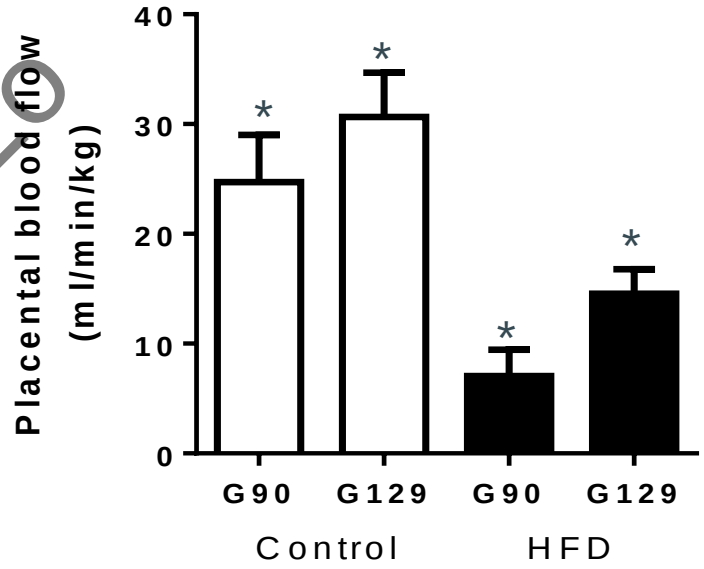
References: *Roberts V,. et al. 2018*

Impact of Maternal High Fat Diet (HFD)

- Japanese macaques
  - Control diet (CON, 14% fat)
  - High-fat diet (HFD, 36% fat)

- Maternal-side placental perfusion was significantly reduced in HFD animals compared to controls apparent both at mid- and late-gestation.

- HFD affects vascular development and blood flow, which may contribute to the increased frequency of stillbirths in pregnancies with maternal HFD consumption



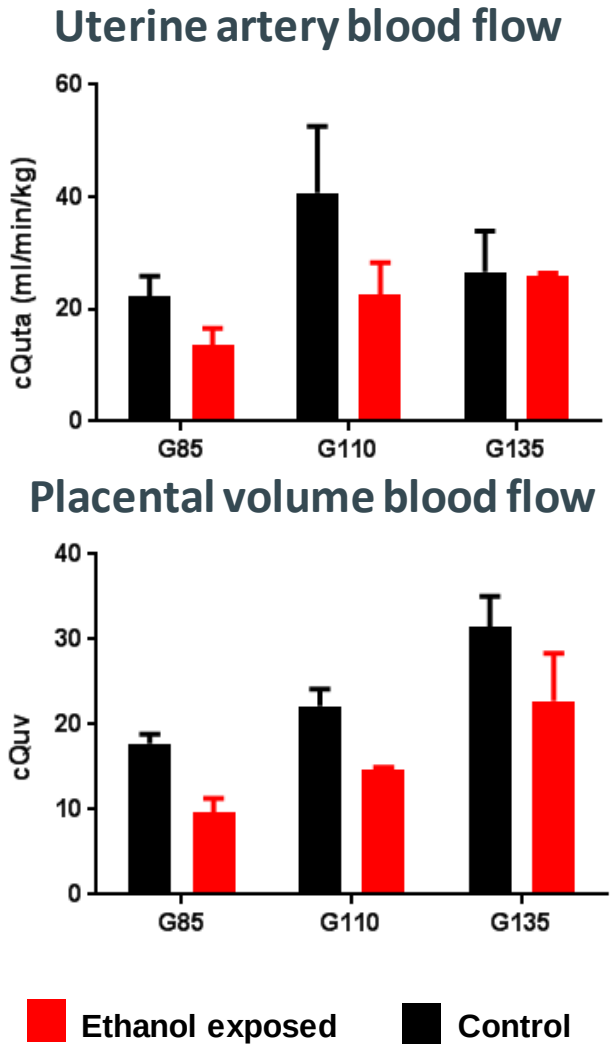
References: *Frias A, et al. 2011*

Effect of Maternal Alcohol Use

- Rhesus macaques
  - Ethanol (1.5g/kg/day, ~6 drinks/day)
  - Control (isocaloric fluid)

- Self-administered ethanol or control fluid preconception through 1st trimester

- Decreased calculated placental volume blood flow and uterine artery blood flow on ultrasound

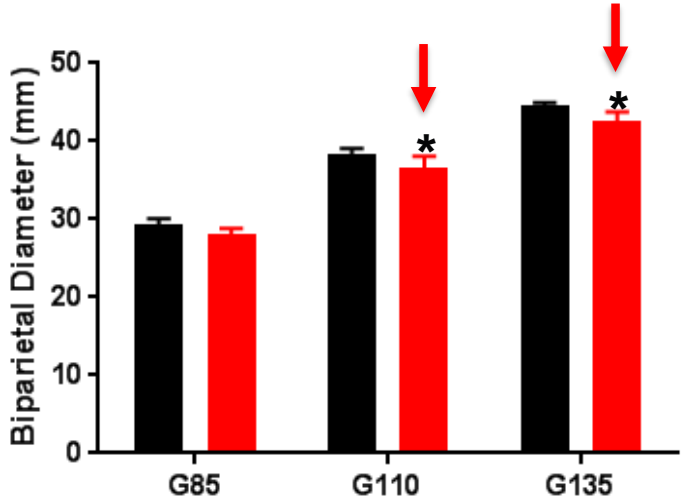


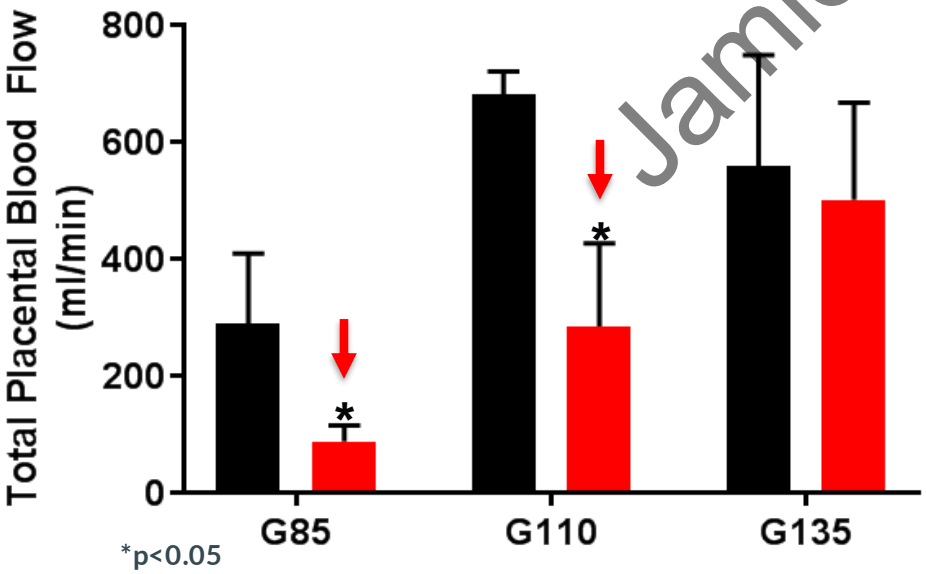
References: Lo et al. AJOG (2017), Frias et al. Endocrinology (2011), Acharya et al. Ultrasound Obstet Gynecol (2007), Acharya et al. Ultrasound Obstet Gynecol (2005)

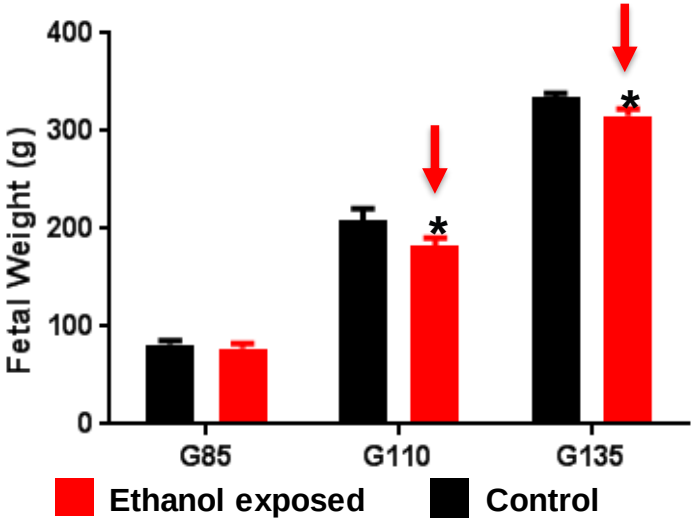
Effect of Maternal Alcohol Use

- Decreased total volumetric placental blood flow and fetal oxygen availability on MRI at early to mid-gestation

- Decreased fetal growth was noted at mid- to late-gestation.





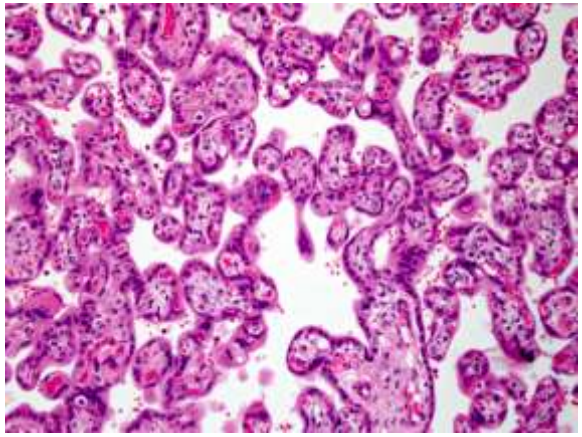


References: Lo et al. AJOG (2017), Frias et al. Endocrinology (2011), Acharya et al. Ultrasound Obstet Gynecol (2007), Acharya et al. Ultrasound Obstet Gynecol (2005)

Placental Infarctions in Ethanol-Exposed

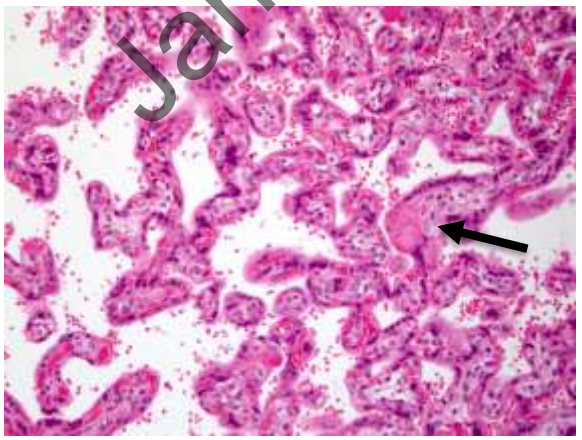
- Significantly increased microscopic (<1cm) infarctions in ethanol exposed animals (5/12) vs. controls (0/12), $p<0.05$
- Microscopic and large infarctions were largely present at G110 and G135

CON

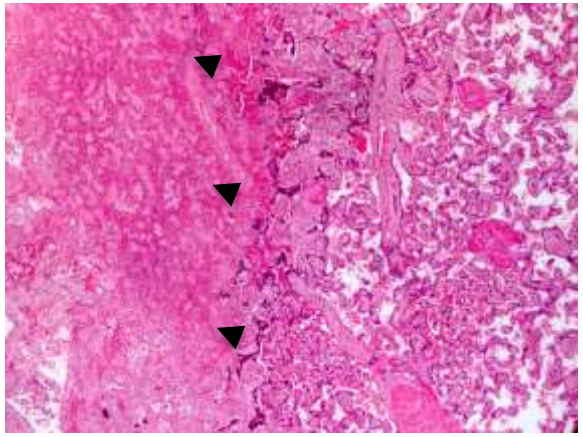


Magnification is 20x

Ethanol Exposed



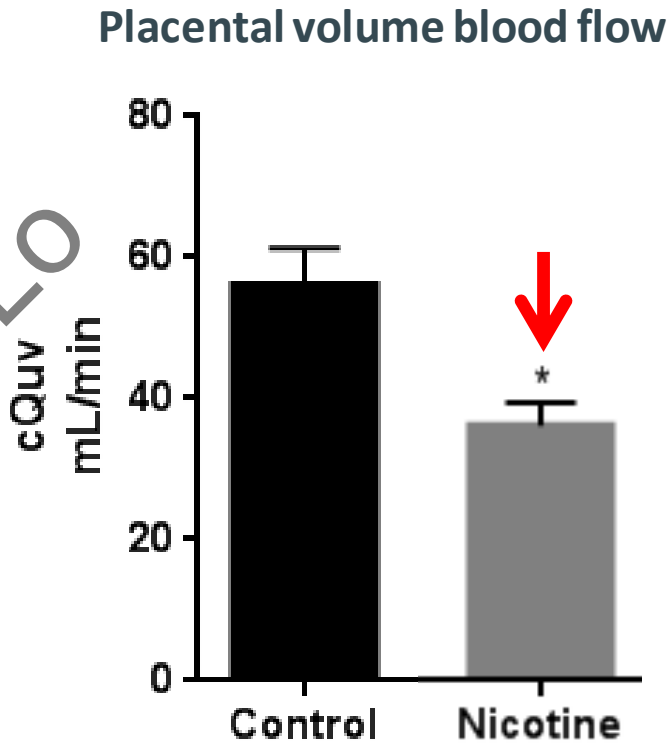
Magnification is 20x



Magnification is 5x

Maternal Nicotine Use

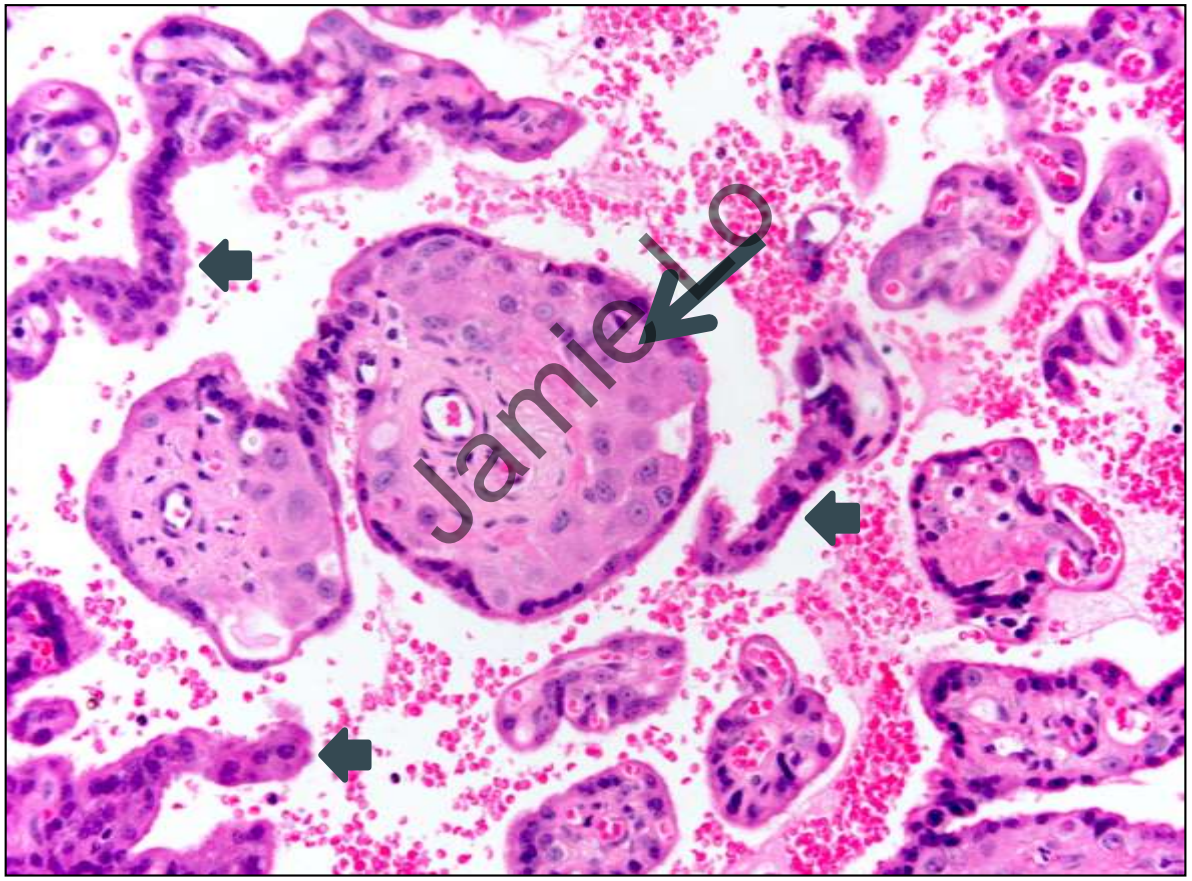
- Rhesus macaques
  - Control
  - Nicotine (2mg/kg/day, ~moderate to heavy smoker)
- Prenatal nicotine exposure is associated with reduced placental volume blood flow on ultrasound



References: *Lo, J et al. 2015*

Maternal Nicotine Use

- Histologic changes of placental hypoxia



References: *Lo, J et al. 2015*

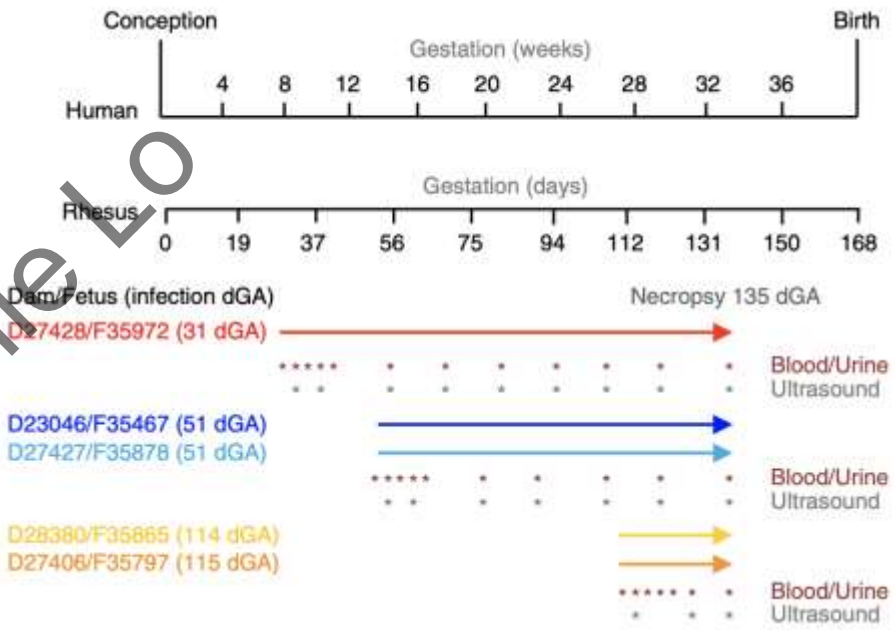
Zika Infection in Pregnancy

- Rhesus macaques (n=5)
  - Infected at gestational days 31, 51, 114, and 115

- Increased microscopic infarctions in all, but large infarctions in cases infected earlier in gestation

- Contrast enhanced ultrasound noted increased flux rate through the spiral arteries into the intervillous space

- Decreased oxygen permeability-surface area



References: *Hirsch, A, et al. 2018*

Summary

- Changes in the maternal environment can impair fetal growth and development that may result in increased susceptibility to diseases in postnatal life.

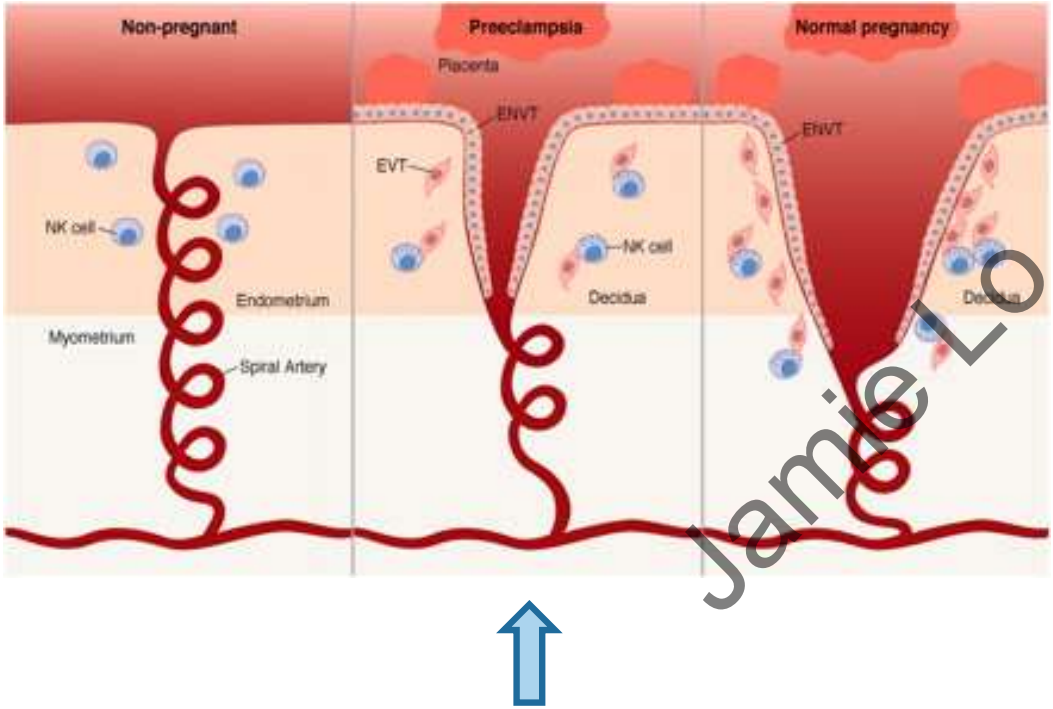
- Placental responses to environmental perturbations are complex and remain poorly understood.

- Intervention strategies to alleviate pregnancy complications and prevent fetal programming of adult disease are likely to be most effective if placental function is targeted

Thank you

Wallowa Mountains, Oregon

Preeclampsia: Leading Theory



- Poor remodeling of spiral arteries
- Low volume, high velocity flow, injuries placenta
- Release of placental debris, inflammatory factors into circulation
- HTN + end-organ injury
- Fetal growth restriction and low amniotic fluid volume

Preeclampsia: Leading hypothesis

Shallow trophoblast "invasion" of maternal spiral arteries contributes to the pathophysiology of preeclampsia.

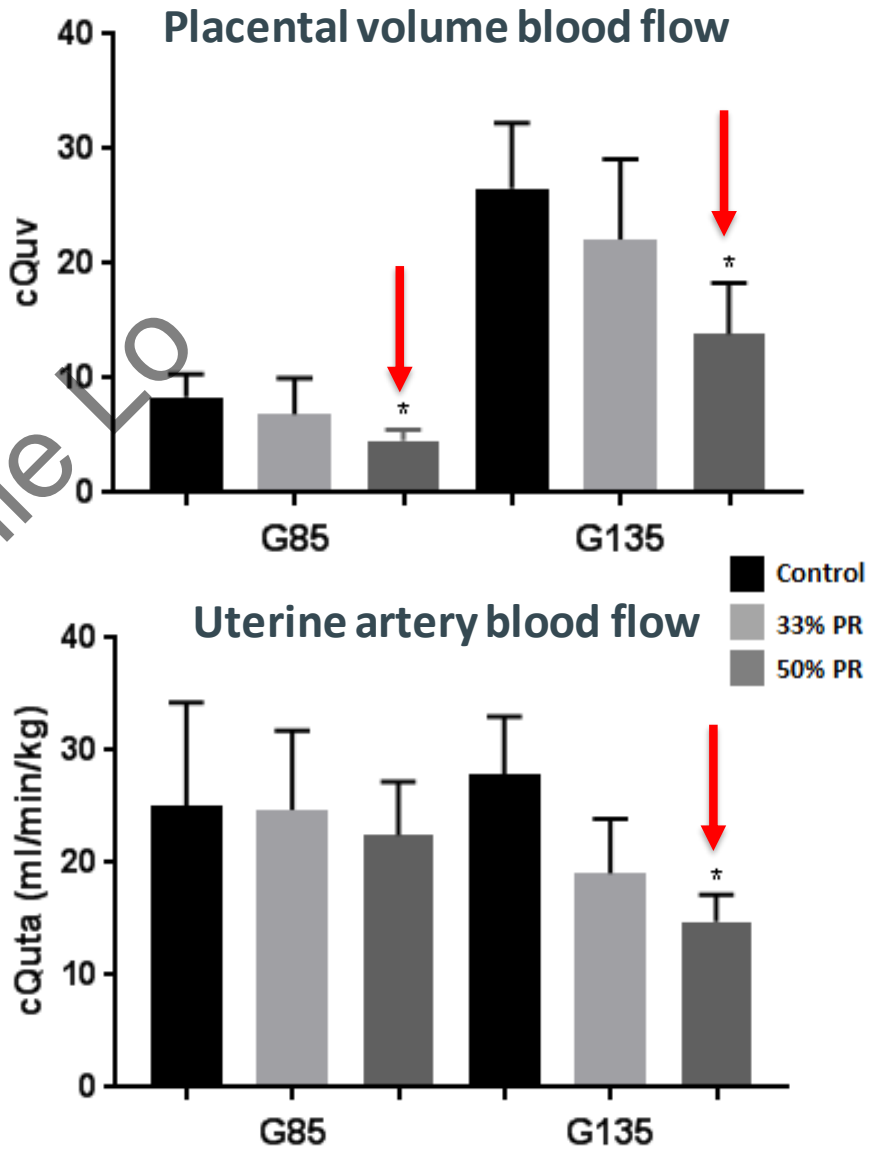
	Normal	Preeclampsia
Velocity	Low	High
Resistance	Low	High
Volume	High	Low

Better approach to watering flowers?

Impact of Maternal Protein Restriction

- Decreased calculated placental volume blood flow in the 50% PR diet group at mid- and late-gestation

- Decreased uterine artery volume blood flow significantly at G135 in the 50% PR diet group



References: *Roberts V,. et al. 2018*