OREGON NATIONAL PRIMATE Research Center

OHSU

Impact of Prematurity on DOHaD

OHSU DOHaD Summer Course, August 12, 2021

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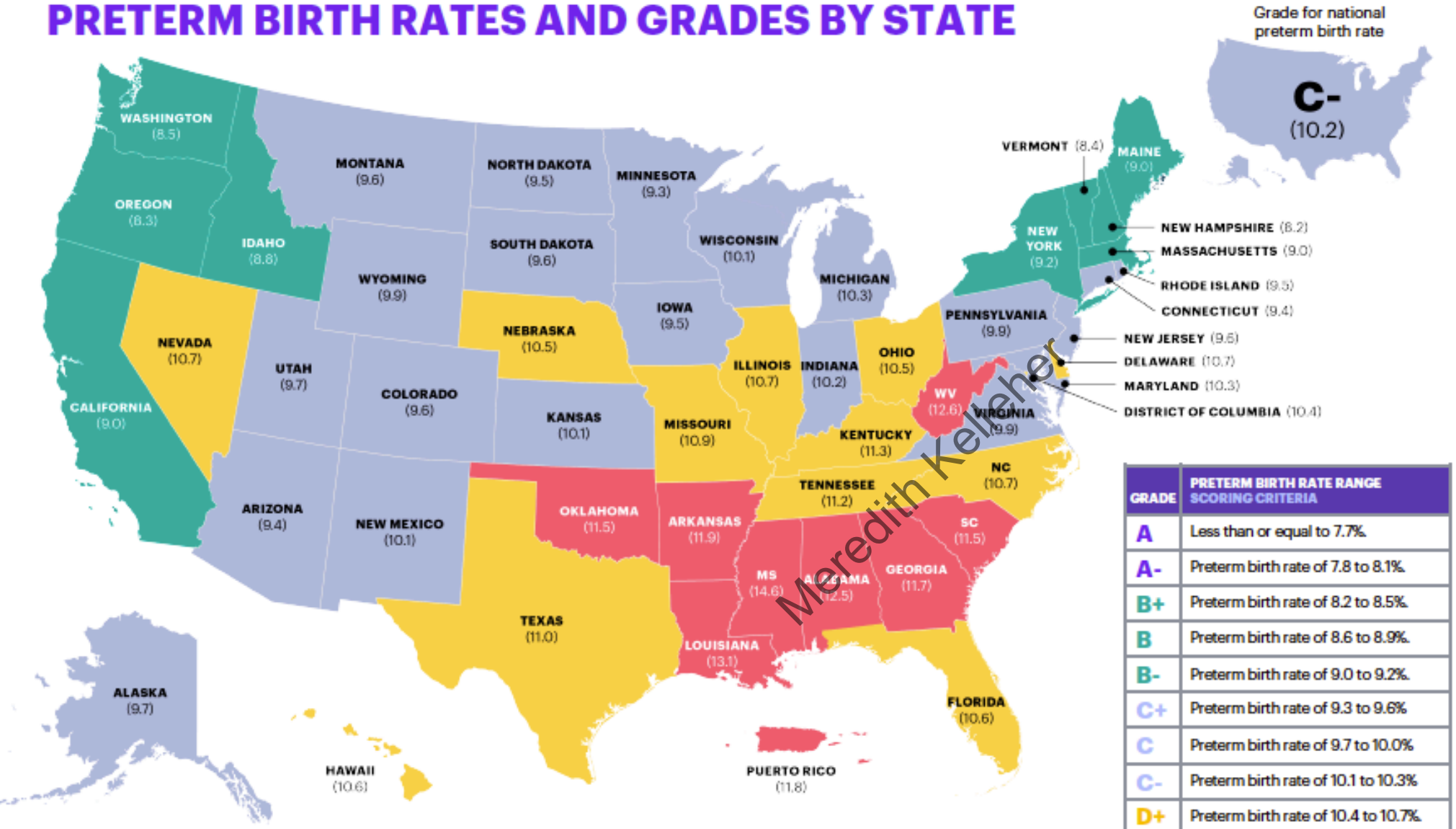
Objectives

1. Recognize the pathophysiological processes and multiple etiologies of preterm birth
2. Describe mechanisms of perinatal developmental injury
3. Identify experimental evidence and epidemiological links between prematurity and non-communicable diseases of later life

Things to consider:

- Separating influence of cause or prematurity from effects of immaturity, low birth weight and medical treatment is very difficult
- Severity of outcomes are greatly affected by gestational age and birthweight but even late preterm/early term delivery are negative

PRETERM BIRTH RATES AND GRADES BY STATE



GRADE	PRETERM BIRTH RATE RANGE SCORING CRITERIA
A	Less than or equal to 7.7%.
A-	Preterm birth rate of 7.8 to 8.1%.
B+	Preterm birth rate of 8.2 to 8.5%.
B	Preterm birth rate of 8.6 to 8.9%.
B-	Preterm birth rate of 9.0 to 9.2%.
C+	Preterm birth rate of 9.3 to 9.6%
C	Preterm birth rate of 9.7 to 10.0%
C-	Preterm birth rate of 10.1 to 10.3%
D+	Preterm birth rate of 10.4 to 10.7%.
D	Preterm birth rate of 10.8 to 11.1%.
D-	Preterm birth rate of 11.2 to 11.4%.
F	Preterm birth rate greater than or equal to 11.5%.

PRETERM BIRTH RATE

10.2%

Puerto Rico is not included in the United States total.

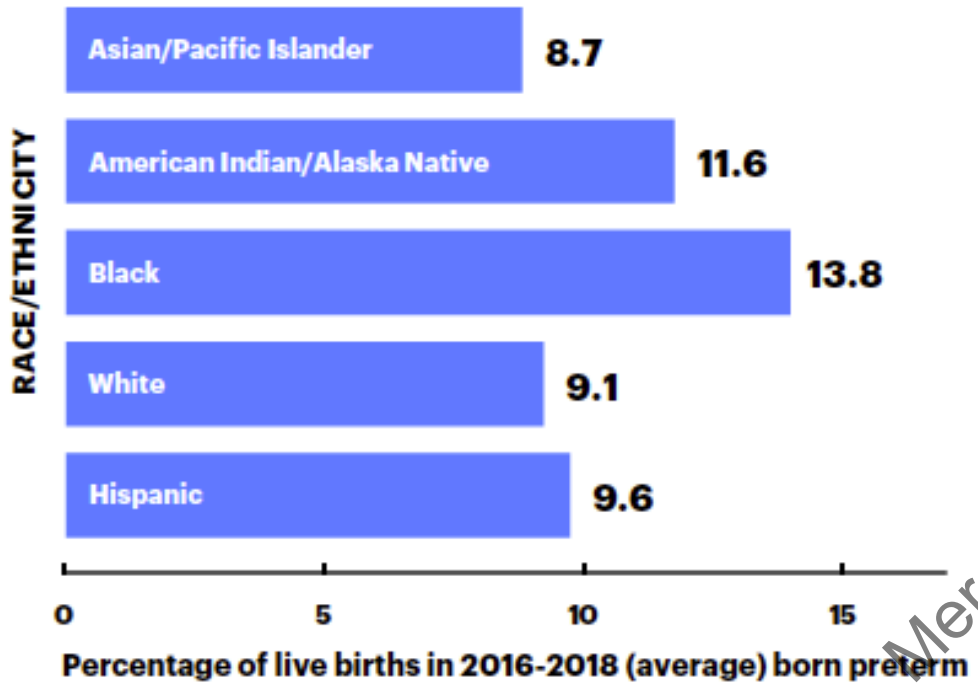
Preterm is less than 37 completed weeks of gestation, based on obstetric estimate of gestational age.

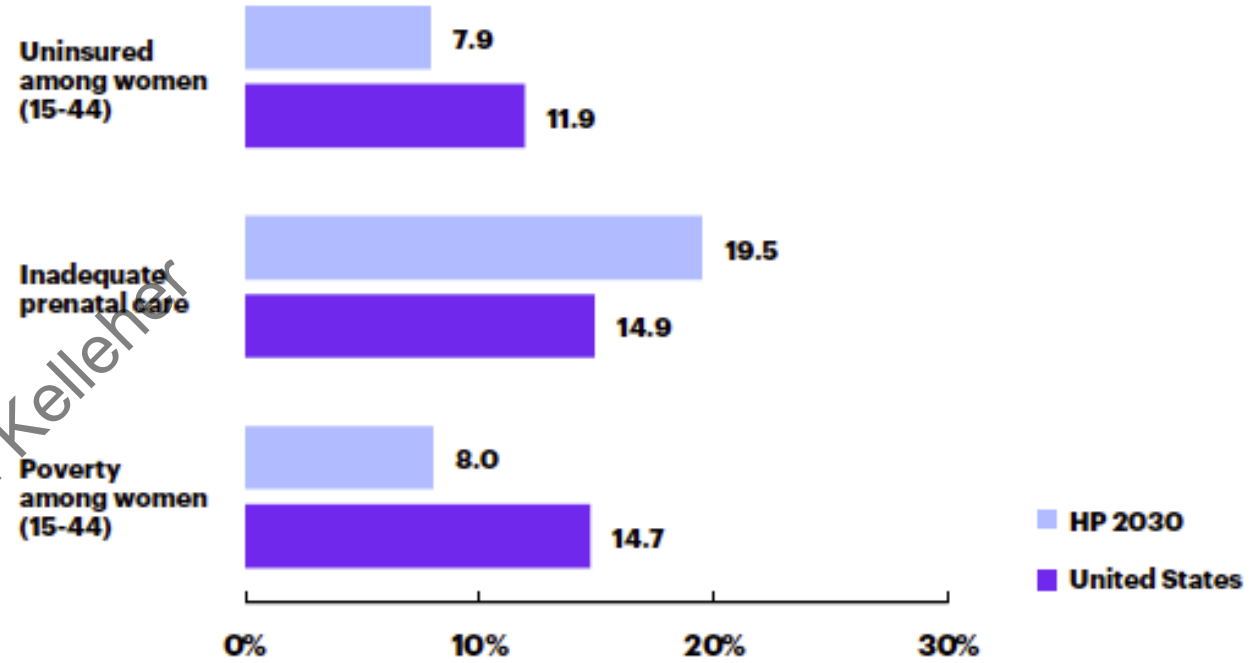
Source: Preterm birth rates are from the National Center for Health Statistics, 2019 final natality data.

Grades assigned by March of Dimes Perinatal Data Center.

MARCH OF DIMES

Social Determinants of Health – Preterm Birth

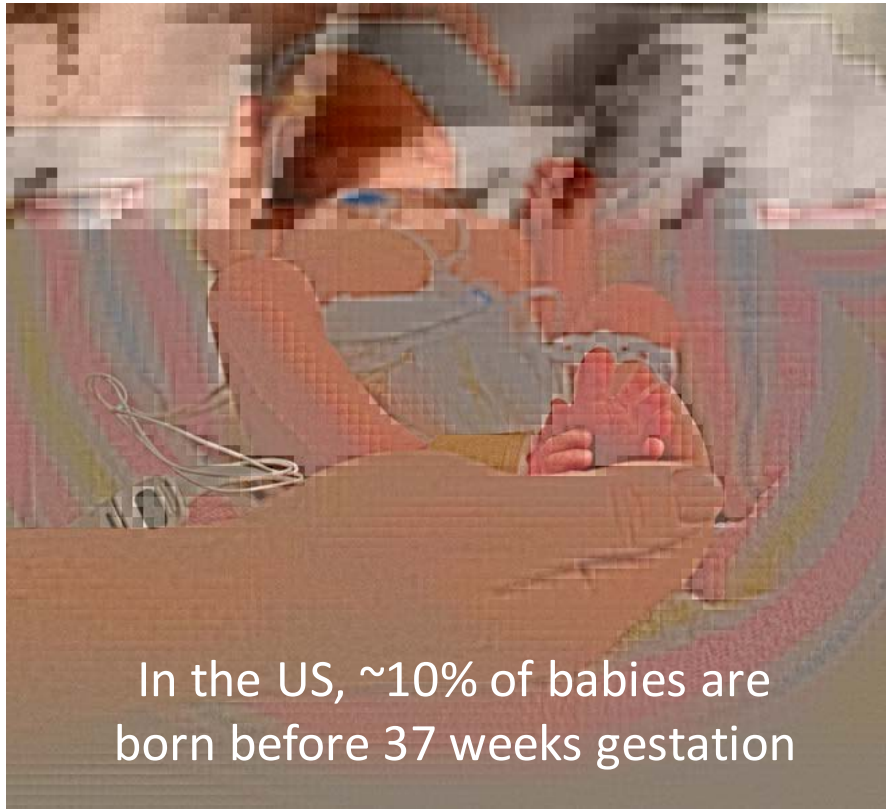


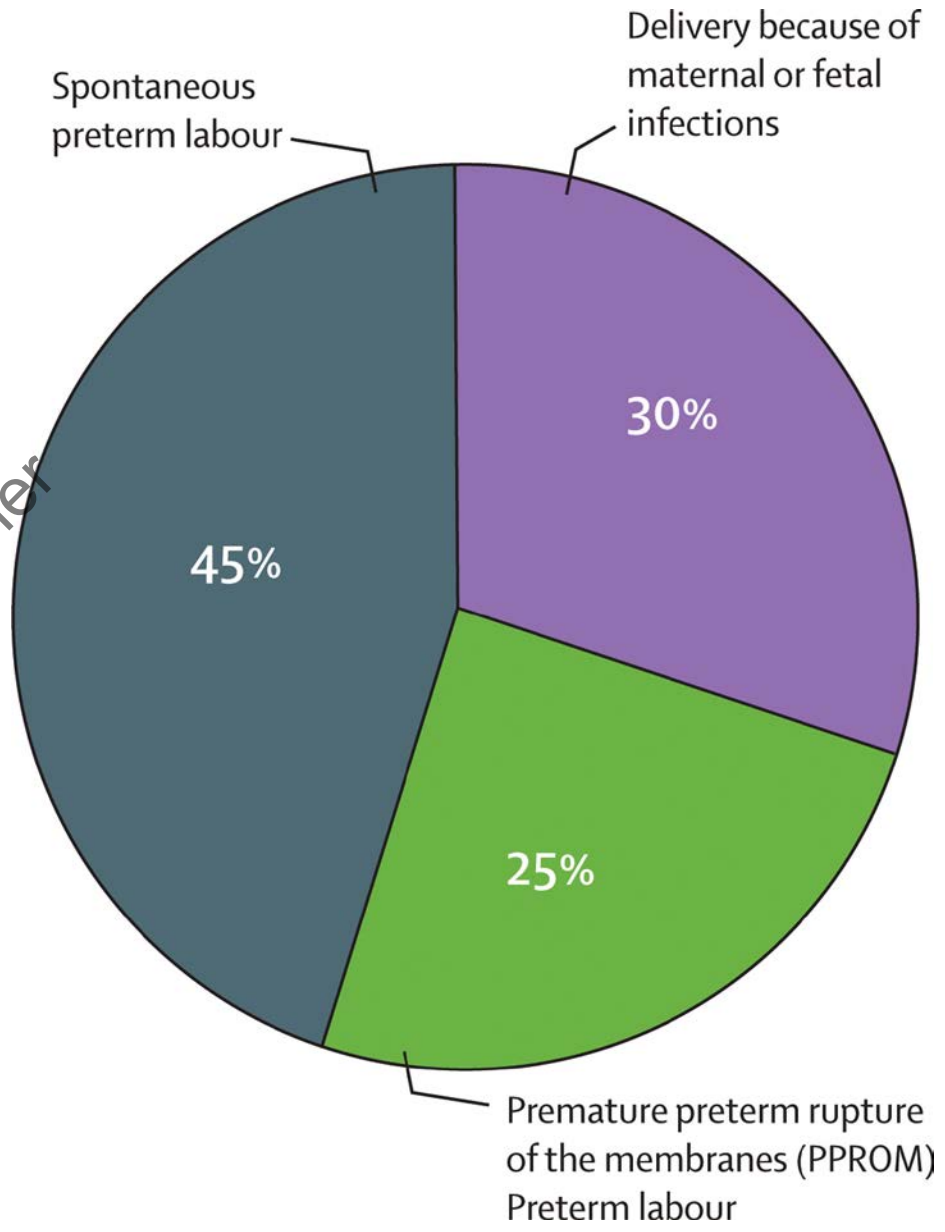


- Structural, systemic and environmental factors
- Access to prenatal and maternal care
- Socioeconomic status
- Maternal age
- Maternal stress
- Short interpregnancy interval
- Educational status
- Marital status
- Physical work, long hours

MARCH OF DIMES

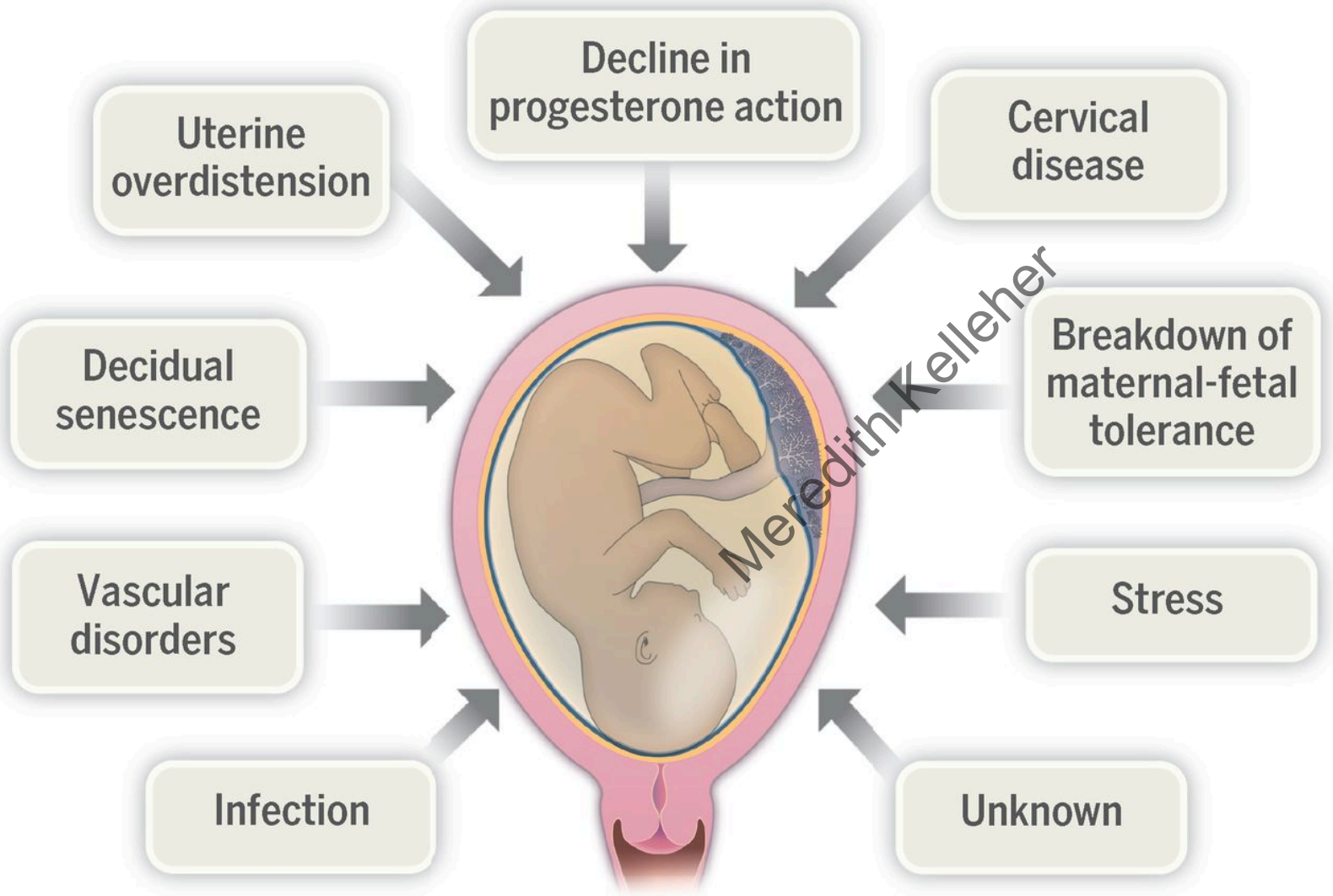
Causes of Premature Birth





Goldenberg *et al*, Lancet 2008 371(9606): 75-84

Proposed Mechanisms of Spontaneous Preterm Labor



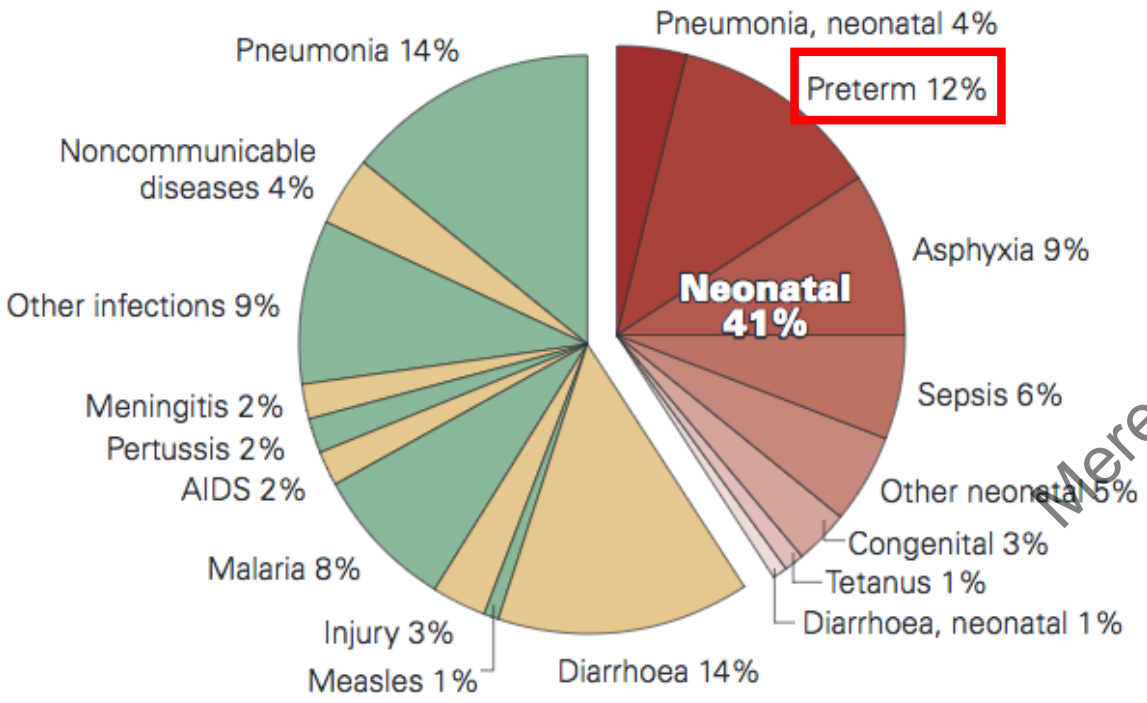
Causes of preterm birth may also differ in incidence by gestational age.

Infection is present in ~40% of births <27 weeks and 15% of births 27-37 weeks gestation.

Roberto Romero et al. Science 2014;345:760-765

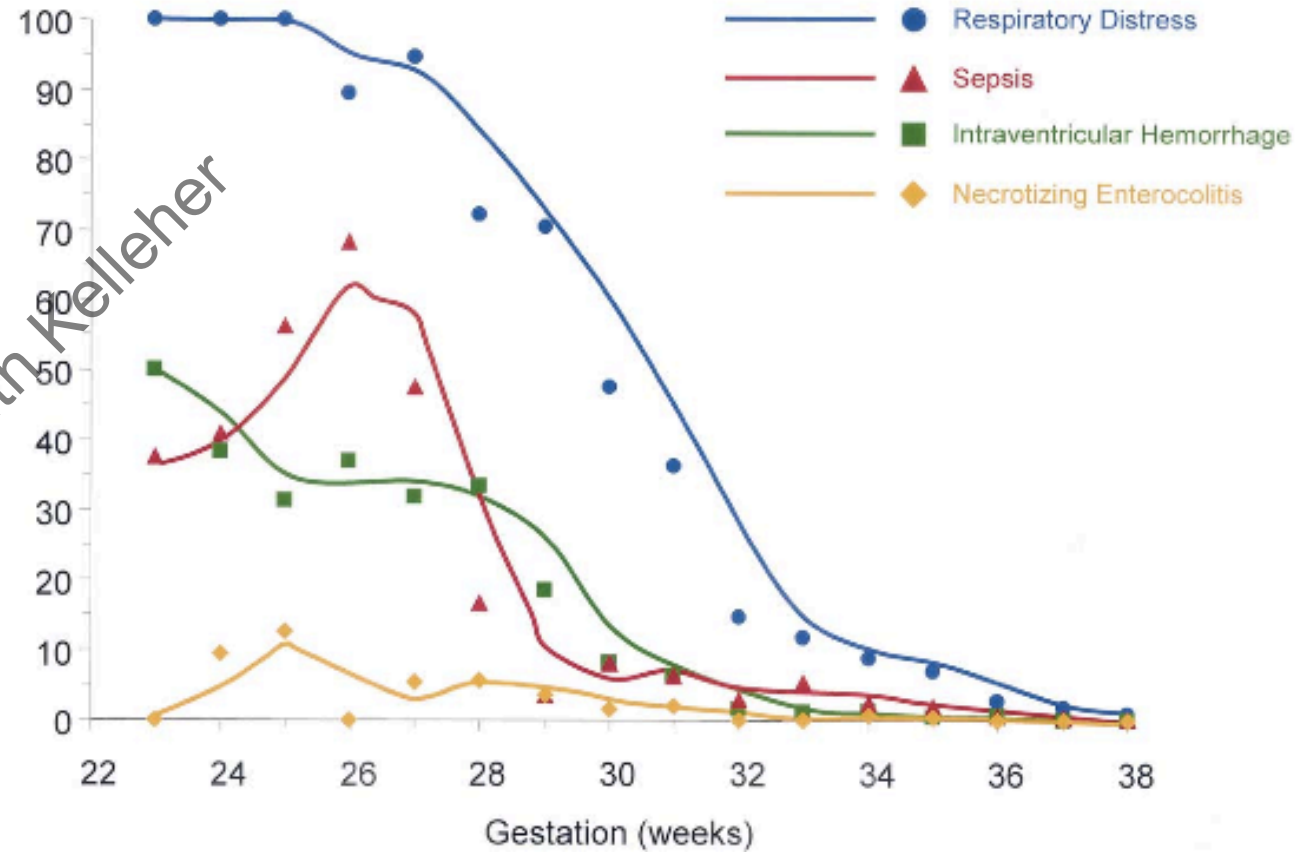
Preterm Mortality and Morbidity

Global Causes of Child Mortality (2008)



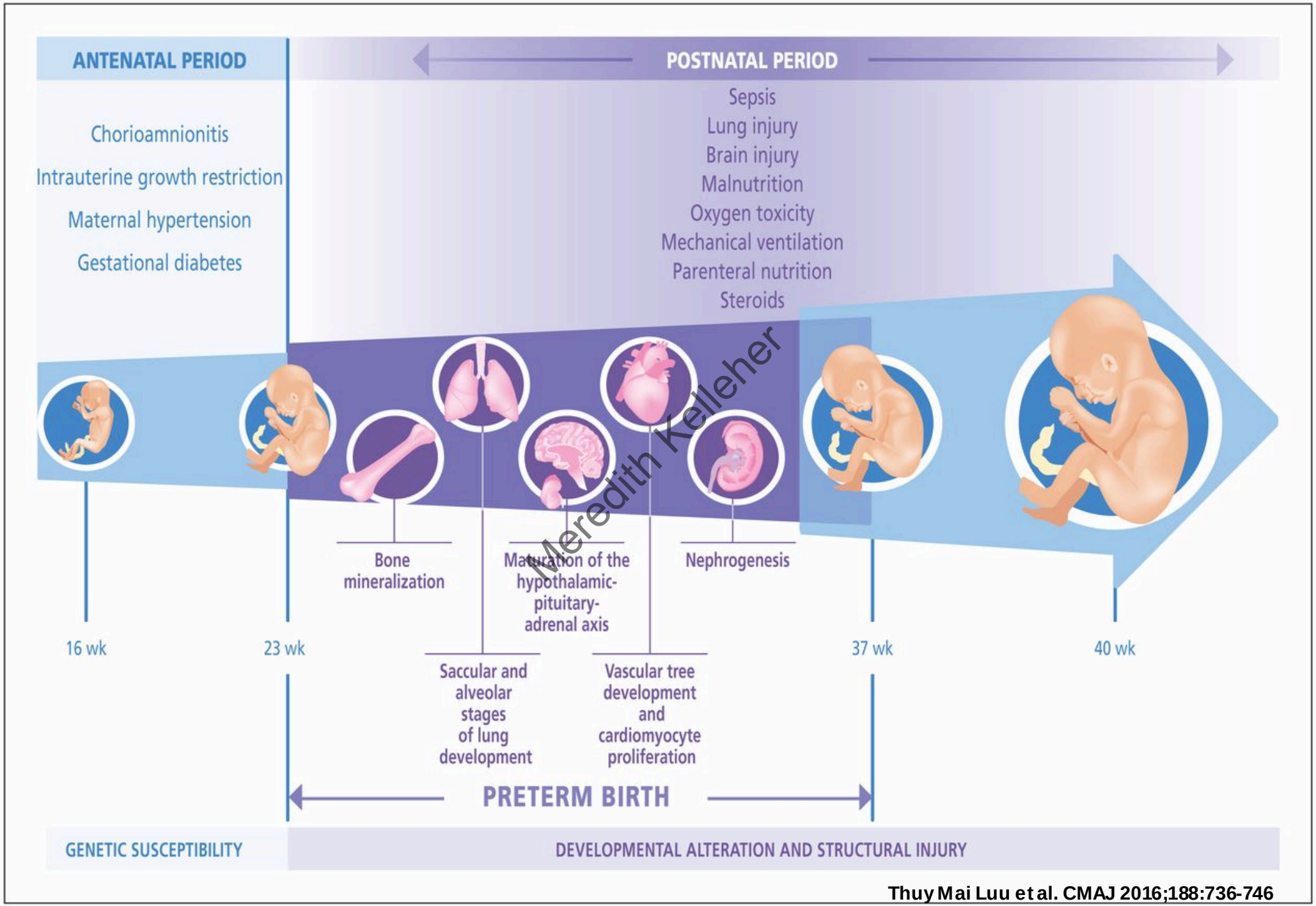
Undernutrition contributes to one-third of child deaths.

Gestational Age at Delivery



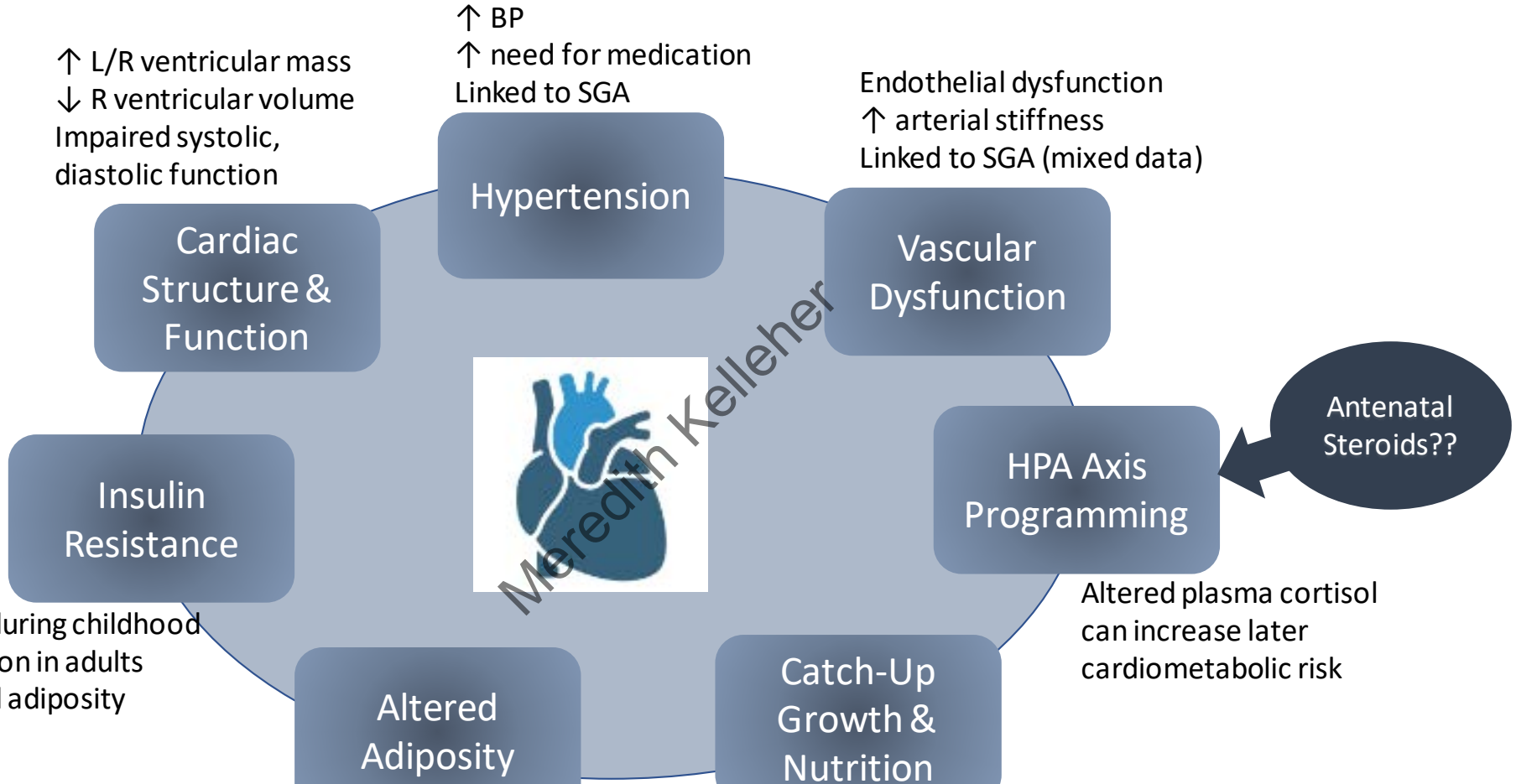
Countdown to 2015: Maternal, Newborn & Child Survival Report, WHO and UNICEF (2010)

Mercer. Treatment of Preterm PROM, Obstet Gynecol, 2003



Thuy Mai Luu et al. CMAJ 2016;188:736-746

Cardiometabolic Disease



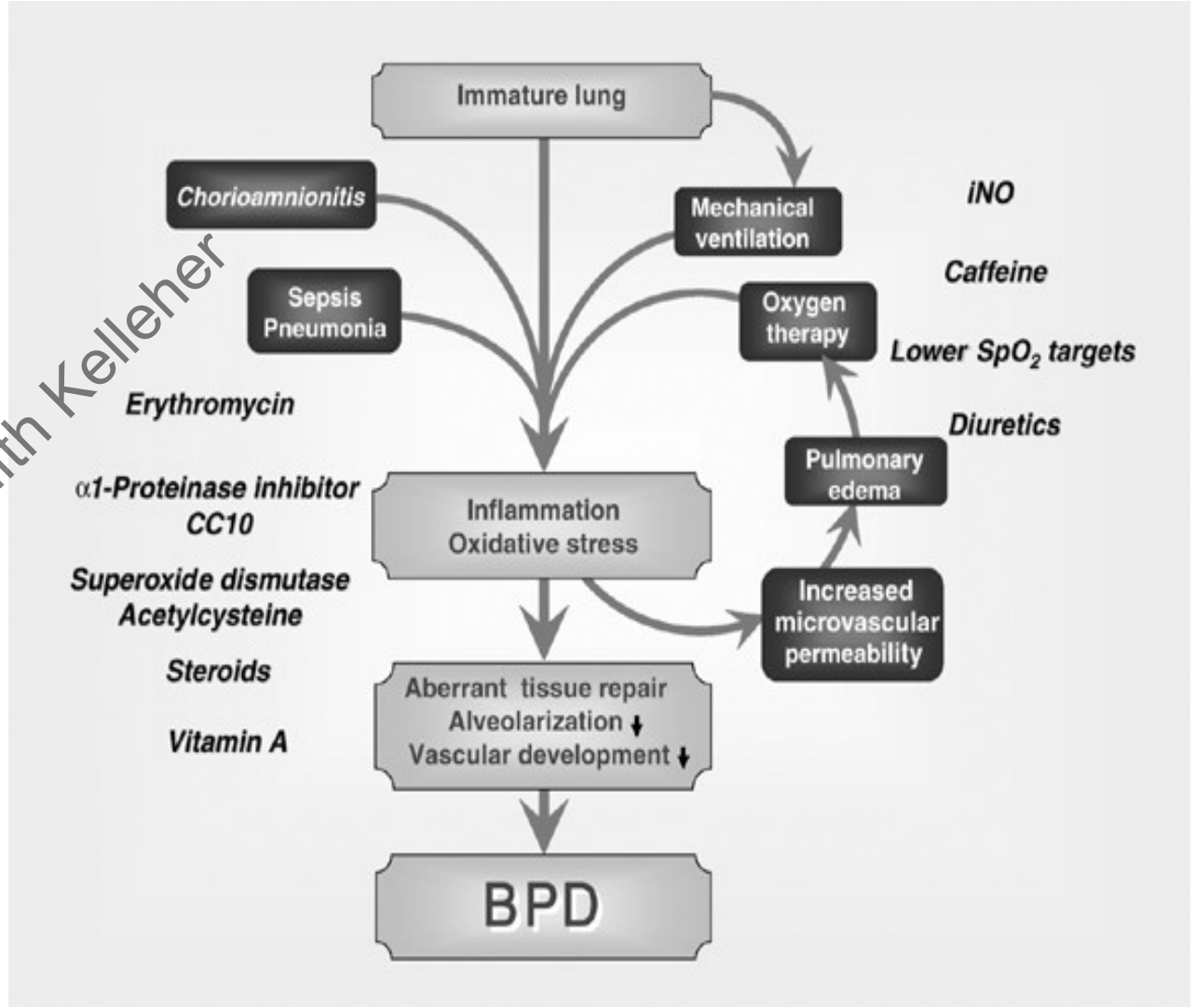
Prematurity has long-term implications for later life hypertension and cardiovascular disease

Risk of Renal Disease with Prematurity

- Systematic review of over 2 million former low birth weight (LBW) infants (often preterm) concludes an odds ratio of 1.73 to develop chronic renal disease (White, 2009)
- Disrupted organogenesis → reduced kidney size and nephron number with 60% of nephrons formed in the 3rd trimester
- Co-morbidities, e.g. placental insufficiency, IUGR and fetal hemodynamic changes, inflammation and ROS also influence organogenesis
- Adaptive microstructural changes in response to disrupted development or insults can include simplification, fibroproliferation and reduced density of capillary networks → predisposes to later chronic kidney disease
- NICU setting → Optimizing cardiorespiratory function, sodium and fluid management and reducing exposure to nephrotoxins (drugs, TPN, hyperoxia and ROS) can improve outcomes and acute kidney injury

Preterm Lungs – RDS and BPD

- Respiratory distress syndrome affects nearly all infants <28weeks gestation; lack of surfactant causes lungs to collapse
- Bronchopulmonary dysplasia is chronic lung disease caused by damage to lungs and alveoli
  - Fewer, enlarged alveoli
  - Less vascularized
  - May have scarring and fibrosis
- Injury during resuscitation and mechanical ventilation
- BPD needs prolonged breathing support and oxygen

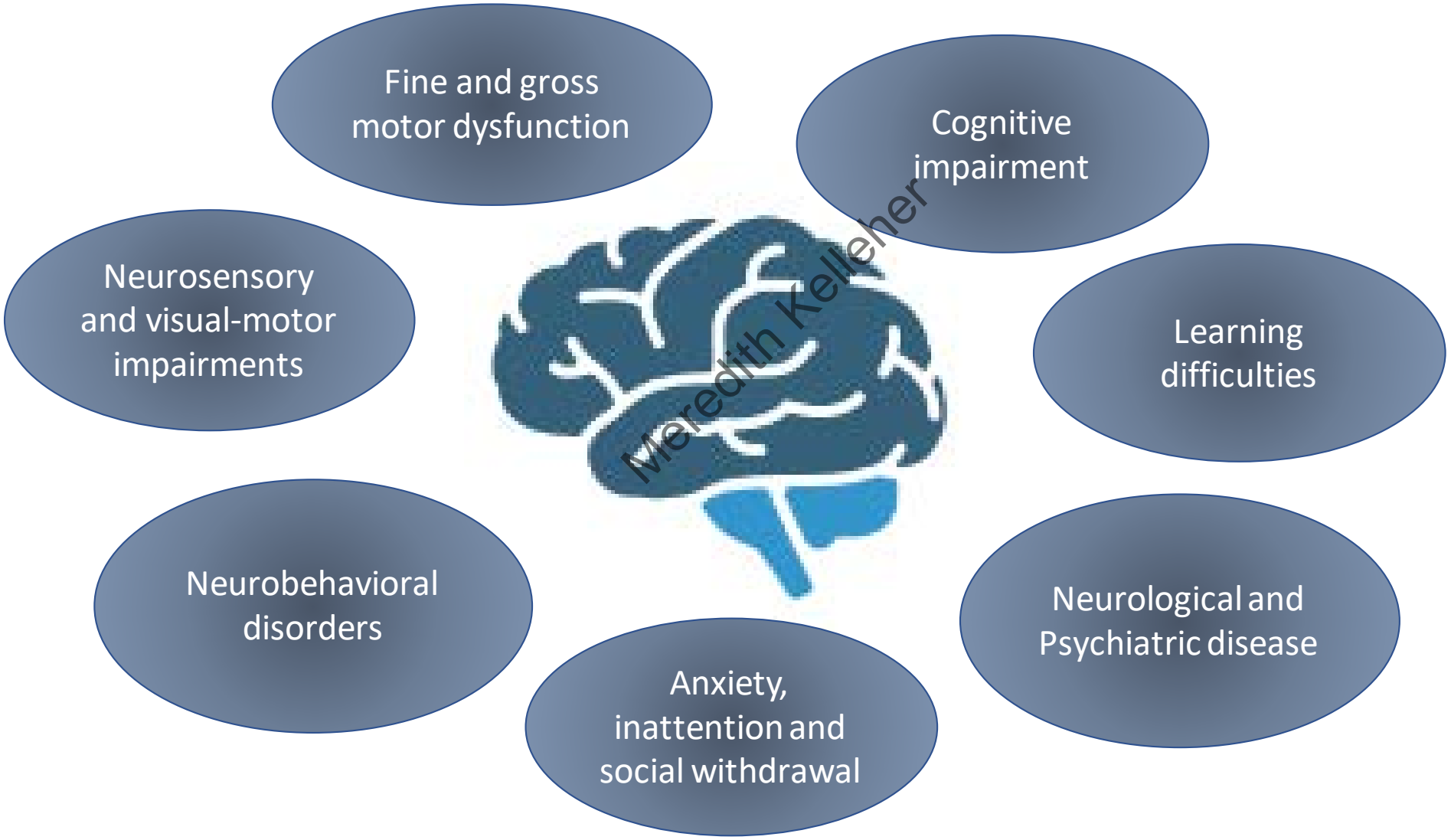


Thomas, W., Speer, C.. *J Perinatol* **27,** S26–S32 (2007).

Chronic Lung Disease

- Infants born <32 weeks gestation are at higher risk of adverse respiratory outcomes and hospitalization into childhood
- BPD, poor growth, infection, inflammation and oxidative stress further increases risk of poor respiratory outcomes into adulthood
- Altered lung structure persists and lung function can decline throughout childhood
- Ex-preterm infants show long-term airflow limitation, decreased gas exchange, increased airway hyperresponsiveness and impaired exercise capacity and are at risk of chronic obstructive pulmonary disease

Neurodevelopmental Disorders of Prematurity



Preterm Brains

- 20-59% of infants born <26 weeks have neurodevelopmental disability
- Even late preterm infants (34-36wks) are at higher risk of cerebral palsy (3x) and academic difficulties compared to full term infants
- Functional outcomes are related to location and severity of the injury
- Cerebral volume (reduced grey and white matter) correlate with later cognitive outcomes in adolescence
- Impaired cognition, neurosensory and motor function (CP) is linked to white matter injury to which the immature brain is particularly vulnerable
- Gestational exposure to stress, environmental toxins or infection and inflammation associated with preterm birth are proposed to interact with genetic and epigenetic factors to predispose to neurobehavioural or neuropsychiatric disorders

Other systems/processes impacted by prematurity

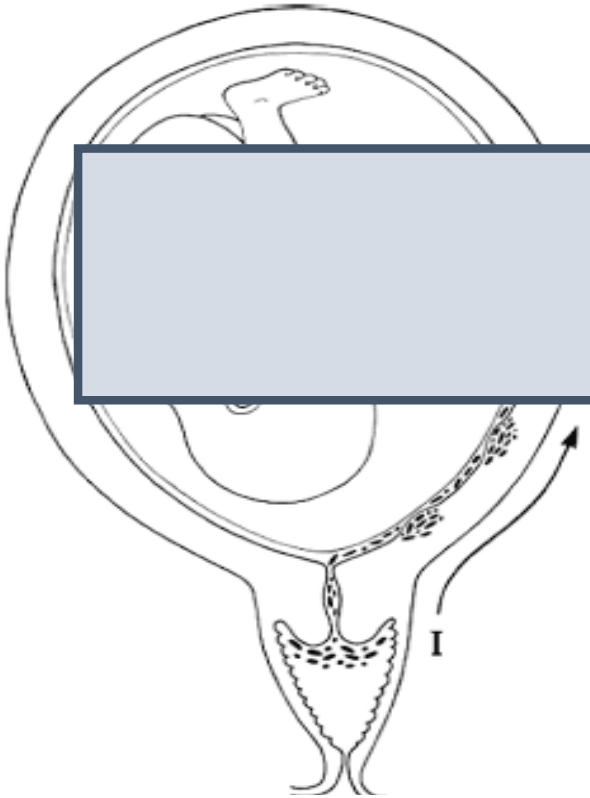
- Endocrine system – HPA axis, stress response, tissue, thyroid, adrenal, pancreatic, pituitary, and placental hormones
- Immune system – increased susceptibility to infection
- Reproductive system – reduced or sub- fertility
- Bone mineralization – increased osteoporosis risk
- Perinatal microbiome – reduced diversity & stability
- Perinatal nutrition and growth

Experimental Model of Preterm Birth

Intrauterine *Ureaplasma* infection in an NHP Model

Intrauterine infection and inflammation leads to preterm labor

Ascending Uterine Infection



Production of Pro-Inflammatory Cytokines

Uterus

Prostaglandin production

Contraction-associated proteins

Cellular Infiltration

Uterine

Ce

Hyaluronidase

Collagenolysis

Dilation

Membranes

Chemokines

Leukocytosis

Prostaglandins

Collagenolysis

Apoptosis

Membrane Rupture

MATERNAL AZITHROMYCIN THERAPY
macrolide antibiotic with anti-inflammatory properties

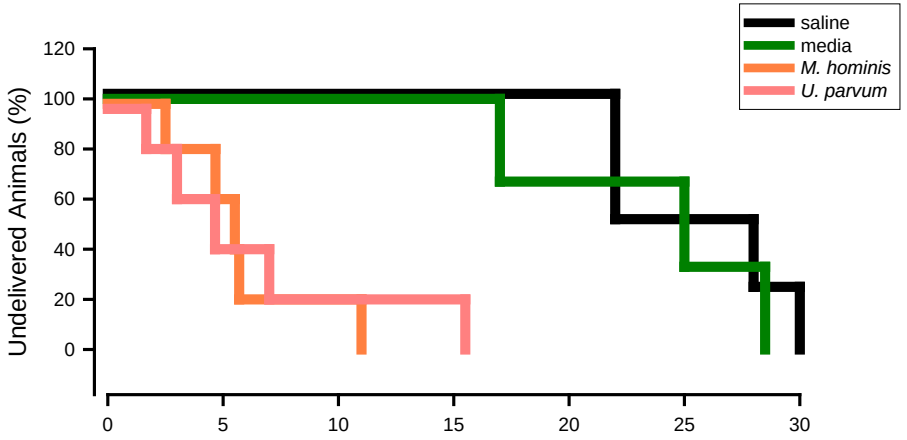
Modified from Keelan JA, Journal of Reproductive Immunology 125 (2018) 89-99

Ureaplasma parvum or *Mycoplasma hominis* as Sole Pathogens Cause Chorioamnionitis, Preterm Delivery, and Fetal Pneumonia in Rhesus Macaques

Miles J. Novy, MD, Lynn Duffy, MT, Michael K. Axthelm, DVM, PhD, Drew W. Sadowsky, PhD, Steven S. Witkin, PhD, Michael G. Gravett, MD, Gail H. Cassell, PhD, and Kenneth B. Waites, MD

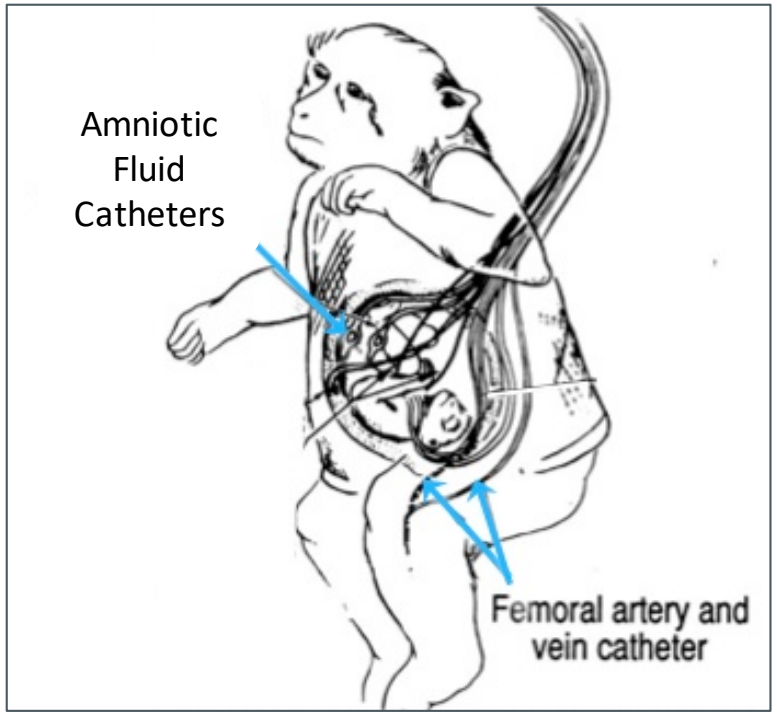
- Intra-amniotic inoculation with *Ureaplasma parvum* (serovar 1)
- Causes preterm delivery
- Fetal lung inflammation and injury

Latency to Delivery after Inoculation



NOVY *et al.*, *Repro Sci* (2009) 16(1):56-70

Antibiotic Treatment of Intra-Amniotic *Ureaplasma* Infection



Catheterized
Time-Mated
Rhesus Monkeys

Sterile Media

Mid-gestation
Intra-Amniotic Infection
(*Ureaplasma parvum serovar 1)*

Saline

Saline

Azithromycin
(25mg/kg/d)

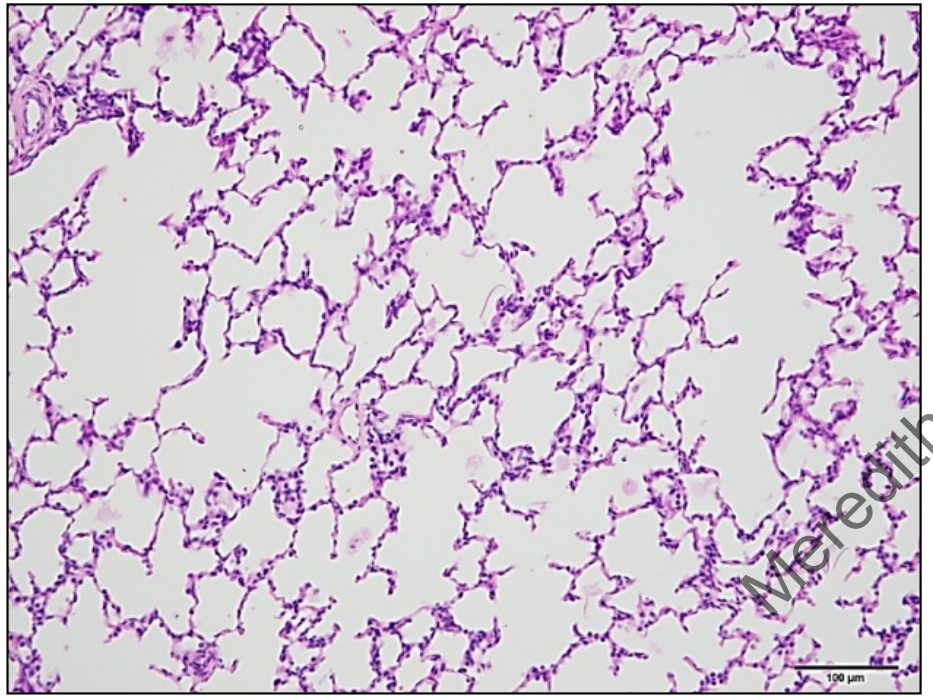
Control

IAI

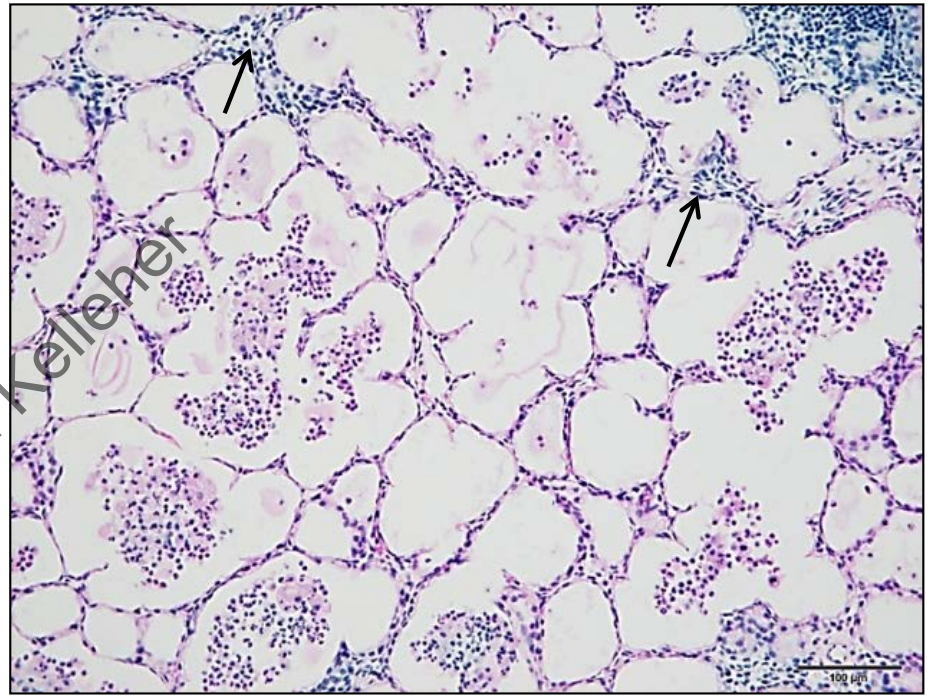
AZI

Ureaplasma Infection and Fetal Lung Injury

Control

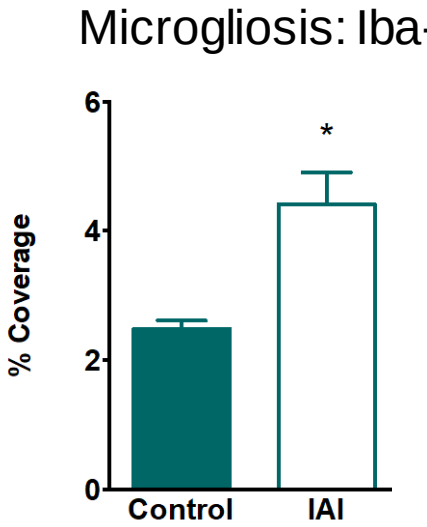


Infection



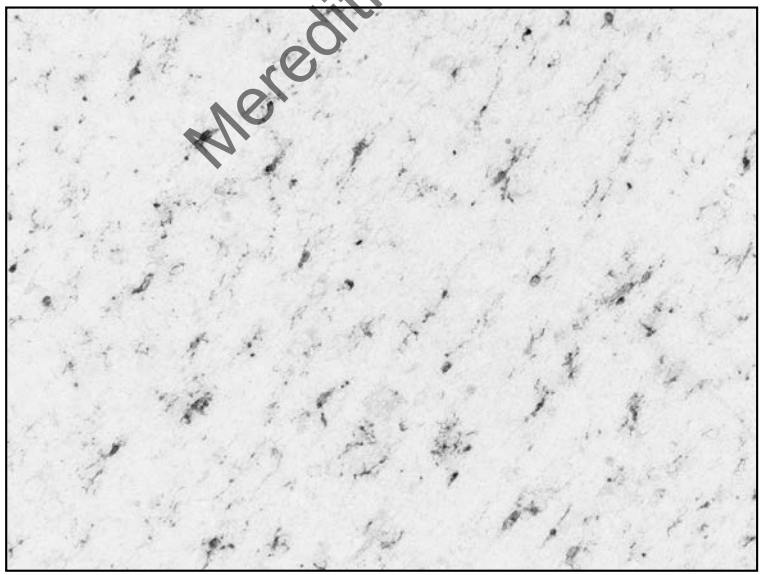
- Inflated fetal lung sections at 150dGA
- Thickened septal walls with prolonged intra-amniotic *Ureaplasma* infection
- Increased cellularity in airway spaces
- Predisposes preterm infant to chronic lung disease, BPD and later life sequelae

Fetal Brain Gliosis after intra-amniotic inoculation

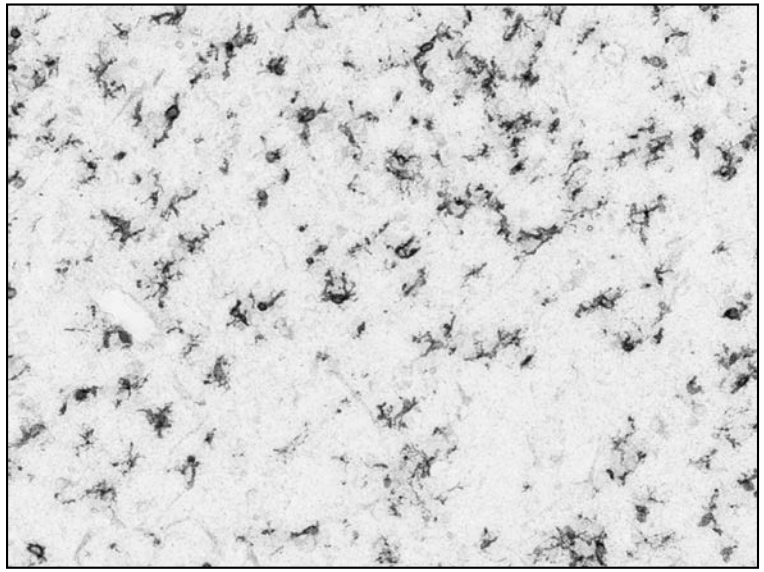


Microglial activation is crucial in the pathogenesis of inflammatory, cytotoxic and free radical-mediated brain injury → significant to preterm neurodevelopmental injury → permanent

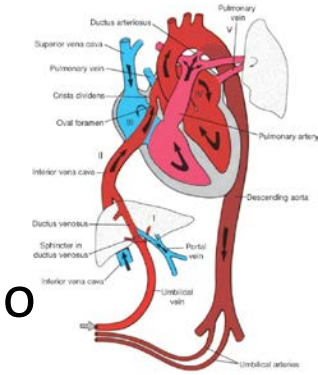
Control



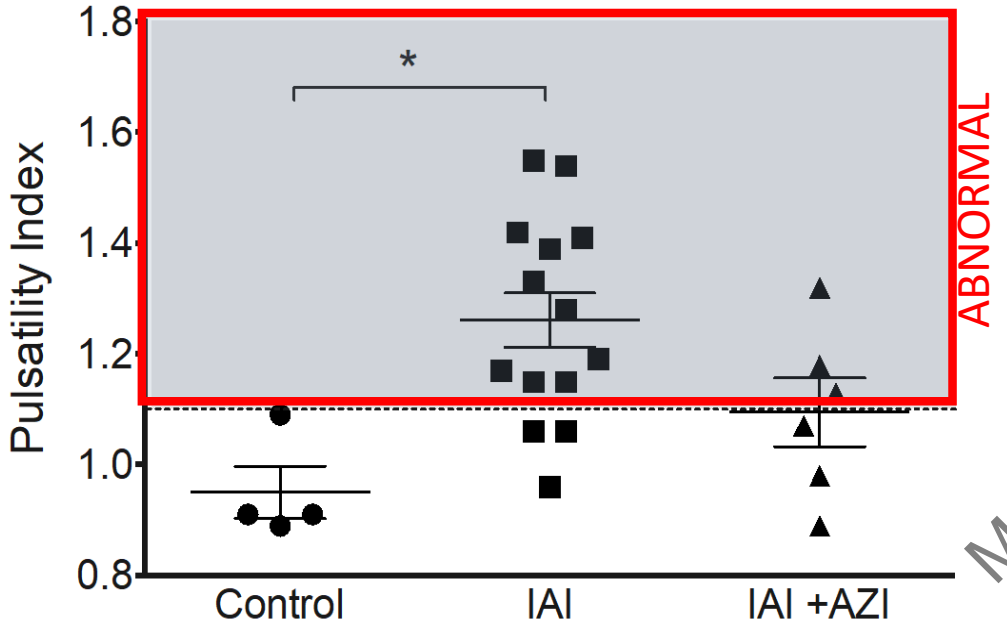
Infection



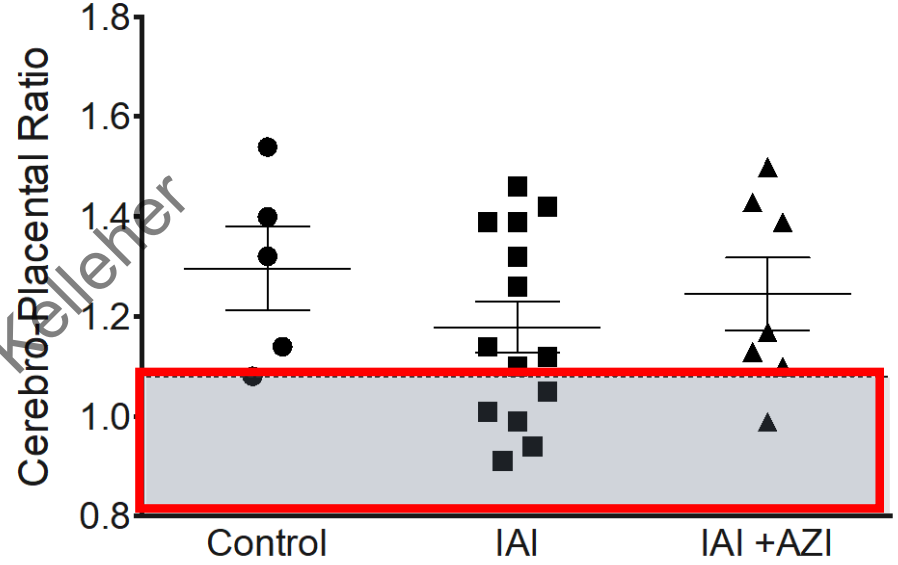
Fetal Hemodynamics



Umbilical Artery Pulsatility Index



Cerebro-Placental Resistance Ratio



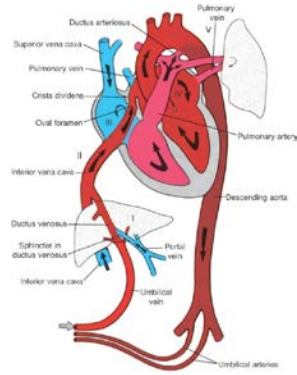
CPR = MCA PI / UA PI *Normal >1 or >1.08 in human literature

- Umbilical artery Doppler reflects downstream vascular resistance within the placenta
- Descending Aorta also had increased PI
- UA PI > 1.1 defined as abnormal in 3rd trimester human pregnancies (Archarya, 2004)

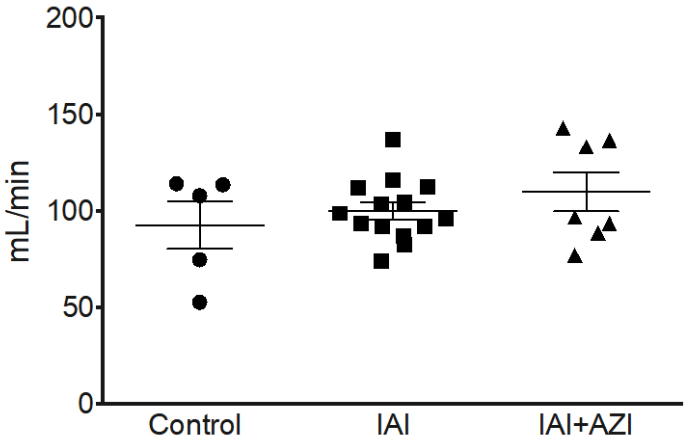
- More animals showed abnormal (reduced) cerebro-placental resistance ratio with infection
- Reduced CPR driven by increased placental resistance rather than reduced middle cerebral artery resistance

Kelleher *et al* (in preparation)

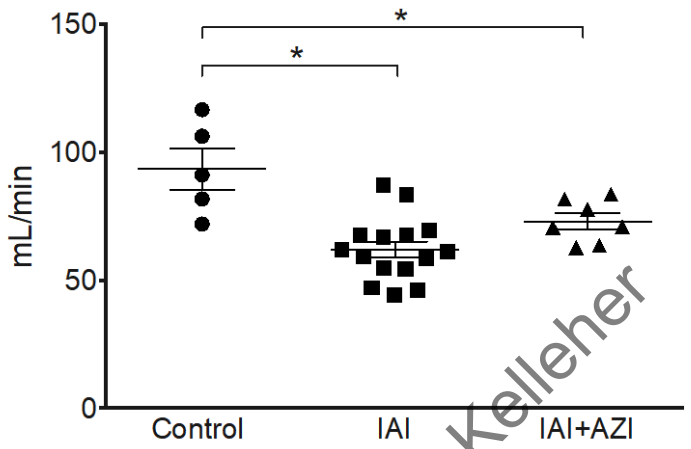
Fetal Cardiovascular Dysfunction



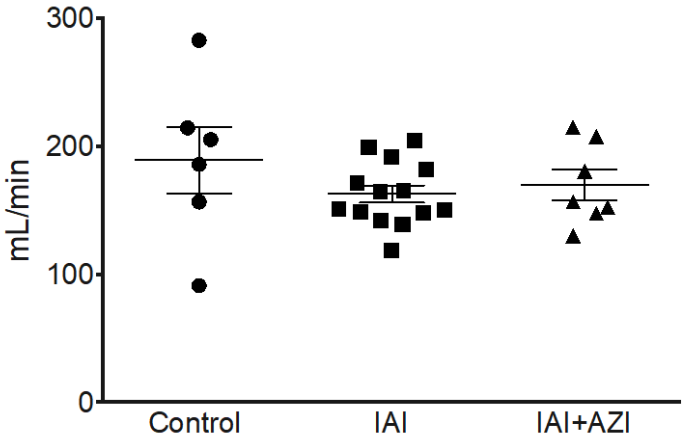
Right Ventricular Cardiac Output



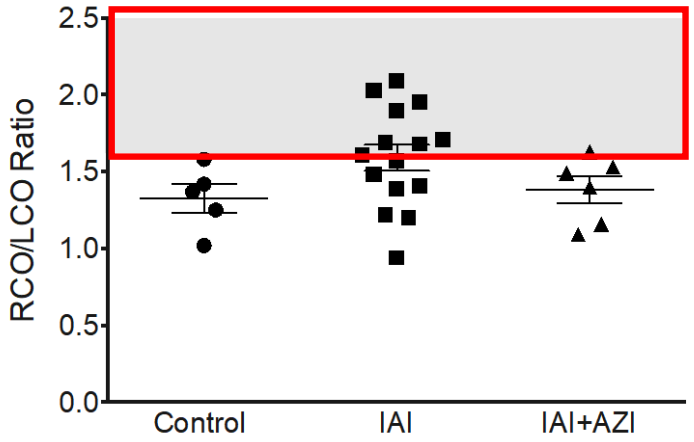
Left Ventricular Cardiac Output



Combined Cardiac Output



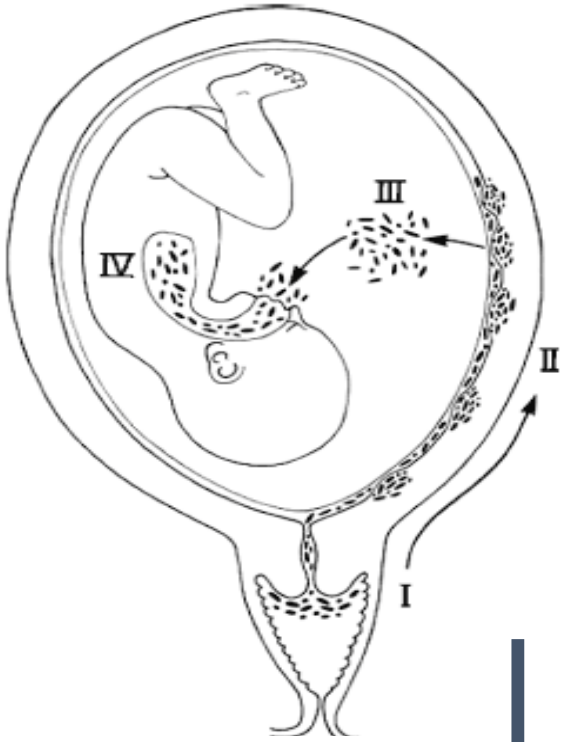
Right/Left Cardiac Output Ratio

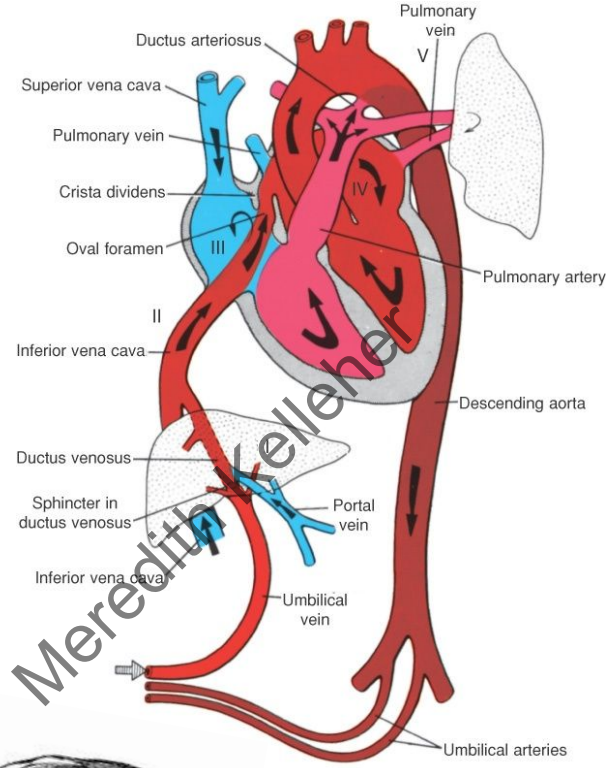


Increased umbilical artery pulsatility index together with decreased left ventricular cardiac output suggests that a disturbance in the placental circulation may lead to reduced left ventricular preload by decreasing pulmonary venous return and predisposing the fetus to hypoxemia.

Kelleher *et al* (2020)

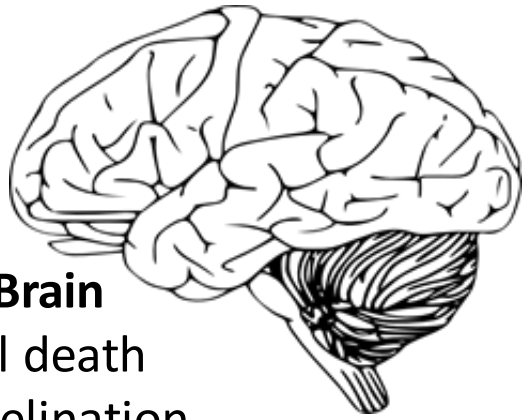
Fetal Sequelae of Infection-Associated Preterm Birth





Fetal Cardiovascular Dysfunction

- Evidence from pPROM + models
- Doppler ultrasound
- Pulsed Doppler echocardiography



Placental Inflammation

- Influences fetal bloodflow
- Pathology/histology
- Inflammatory gene expression

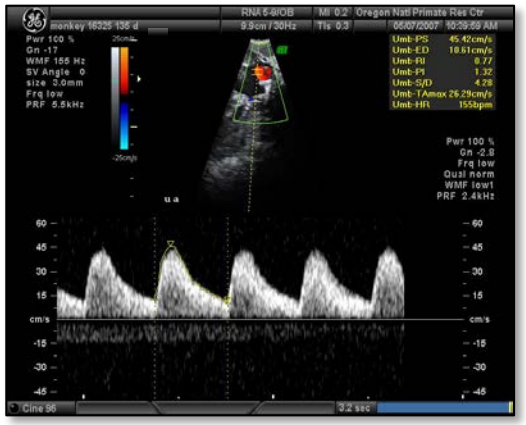
Fetal Brain

- Cell death
- Myelination
- Astroglia
- Microglia

Translational value of maternal-fetal and postnatal NHP studies

- Mechanisms of fetal inflammation and injury
- Applicable to study of developmental disorders, infection and toxicant exposure
- Translational modeling of medical interventions at delivery
- Long-term cognitive, behavioral and functional development

Maternal-fetal period → Birth → Neonatal Transition → Postnatal Development → Long-term development




Kelleher *et al* (2017) Ped Res. 82(2):244-52

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