

Intrauterine blood pressure  
programming by maternal iron  
status: *lost in translation?*

Mandy Brown Belfort, MD MPH

Children's Hospital Boston

Harvard Medical School

# Overview

- Developmental origins of health and disease paradigm
  - Animal models
  - Human epidemiologic studies / use of biomarkers
- Example: study of maternal iron status and offspring blood pressure
  - Translation from animal model to human population

# Developmental Origins of Health and Disease

- Paradigm that emphasizes prenatal period and early childhood as important periods for development of chronic disease throughout life
  - Developmental programming = perturbation at a critical period of development causes alterations with lifelong consequences

# Developmental Origins of Health and Disease – Animals

- In animals models, perinatal programming of hypertension and other outcomes well-established
  - Across species
    - Rats, mice, guinea pigs, sheep, non-human primates
  - Relatively easy to induce
    - Nutritional
    - Hormonal
    - Utero-placental blood flow (uterine artery ligation)

# Developmental Origins of Health and Disease – Animals

- Animal studies provide proof of principle
- Translation to humans?
  - Exposures typically out of physiologic range
  - Suggest pathways / mechanisms

# Developmental Origins of Health and Disease – Epidemiology

- Study designs
  - Historical cohorts – retrospective
  - Old prospective cohorts (CPP)
  - Offspring follow up of pregnancy RCT's
  - New prospective cohorts (Project Viva)

# Developmental Origins of Health and Disease – Epidemiology

- Limitations
  - Confounding limits causal inference
  - Measurement error can inflate or deflate
    - Magnitude
    - Precision
  - Long latency between exposure and outcome
    - Cohort may outlive investigators
    - Loss to follow-up

# Developmental Origins of Health and Disease – Value of Biomarkers

- Limitations
  - Confounding limits causal inference
    - Biomarkers of pathway/mechanism can provide biological plausibility
  - Measurement error can inflate or deflate
    - Biomarkers can provide better measures, or validation, of exposure or outcome
  - Long latency between exposure and outcome
    - Biomarkers can provide surrogate outcomes

# Developmental Origins of Health and Disease – Biomarkers

- Sources of material
  - Mother/child
    - Blood, urine, hair, nails, fat, saliva
  - Fetus
    - Cord blood
  - Placenta

# Developmental Origins of Health and Disease – Biomarkers

- Better exposure measures
  - Selenium in nails vs. diet assessment
- Different exposure measures
  - Vitamin D in blood = sun + diet → mechanism
  - Vitamin D in diet = dietary recommendations
- Validation of self-report
  - Fatty acids in plasma, RBC's

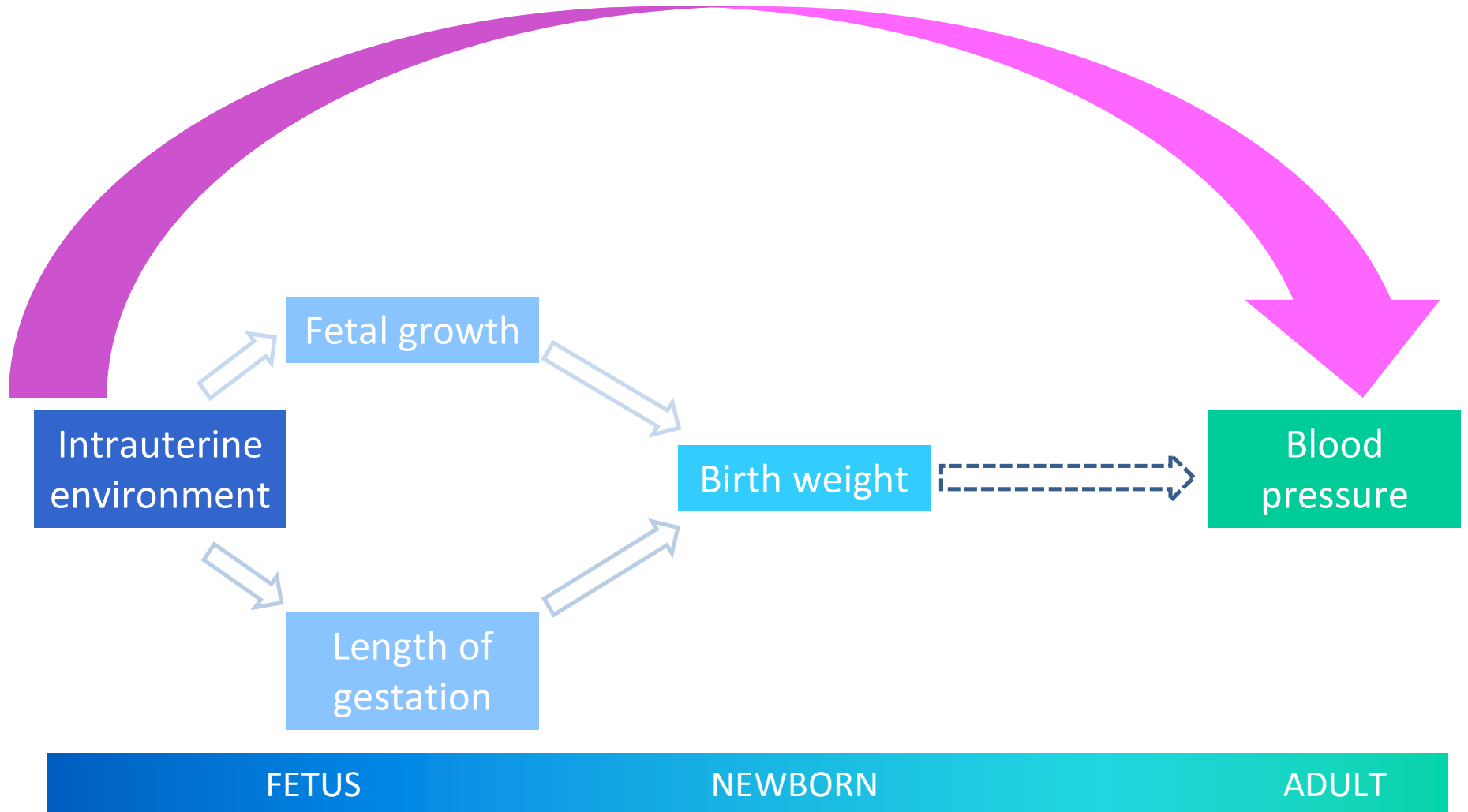
# Developmental Origins of Health and Disease – Biomarkers

- Compliance
  - RCT's of drugs, supplements
- Mechanisms/mediators
  - Salivary cortisol
  - Placenta, cord blood hormones
- Surrogate outcome
  - Fasting plasma insulin predicts CVD

# Hypertension

- Affects ~1/3 of U.S. adults
- Major risk factor for cardiovascular disease
- High societal costs
  - \$76.6 billion in health care & missed work in the U.S.
- Developmental perspective may inform novel approaches to prevention
  - Need more information about specific prenatal exposures that influence blood pressure in offspring

# Intrauterine blood pressure programming: conceptual model

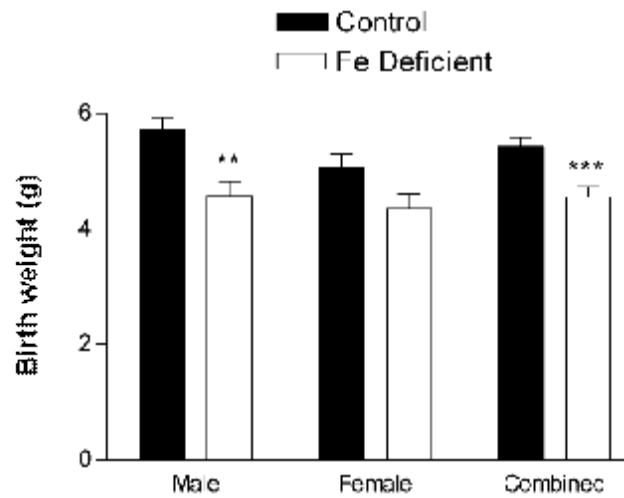


# Intrauterine blood pressure programming: animal models

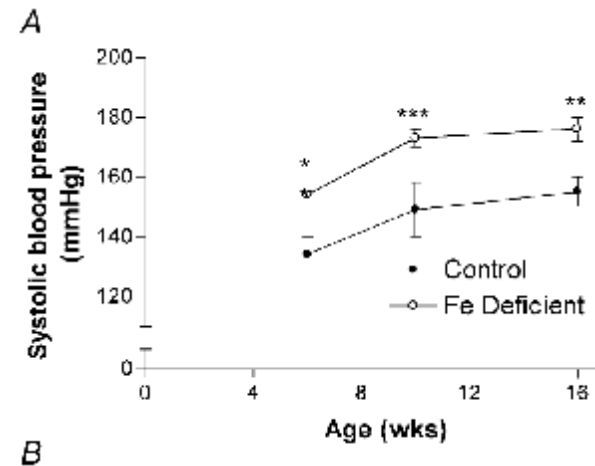
- Maternal under-nutrition
  - Calories
  - Protein
  - Iron
- Hormonal
  - Glucocorticoids
- Utero-placental insufficiency
  - Uterine artery ligation

# Animal model: maternal iron restriction in pregnant rat leads to

Lower birth weight



Higher blood pressure



# Maternal iron restriction and offspring blood pressure: relevance to humans

- Large physiologic demand for iron
  - Expansion of maternal RBC mass by ~20%
  - Growth of fetal, placental, maternal tissues

# Maternal iron restriction and offspring blood pressure: relevance to humans

- Demand difficult to meet through diet
  - 12% of U.S. women 20-49 years are iron deficient
  - 30% of low income U.S. women in 3<sup>rd</sup> trimester of pregnancy have iron deficiency anemia

# Maternal iron status and offspring outcomes

- Observational studies suggest that maternal anemia associated with shortened gestation, small for gestational age, LBW
  - Confounding, other limitations
- RCT evidence that iron supplementation leads to increased birth weight and length of offspring
  - Particularly in groups with higher prevalence of anemia

# Aim

- To examine associations of maternal iron intake and status with offspring blood pressure at 3 years
  - *Hypothesis: poorer iron intake and status associated with higher offspring blood pressure*

# Population & study design

- Project Viva (n=2128)
- Women recruited at 1<sup>st</sup> prenatal visit
- Followed through pregnancy and with children at 6 months, 3 years (*currently 7 years*)
  - Interviews, questionnaires, anthro, blood, hair
  - EMR data
- Domains
  - Perinatal health / nutrition
  - Obesity / cardiovascular disease
  - Asthma
  - Cognition



# Maternal iron status

- 1<sup>st</sup> and 2<sup>nd</sup> trimester
- Iron intake
  - from foods and supplements
  - FFQ with extra supplement questions
- Hematologic measures
  - Hemoglobin, low in later stage of iron deficiency
  - MCV, declines in earlier stage of iron deficiency
  - From clinical lab database
  - Ordered on same date as other screening labs

# Child blood pressure

- Measured x 5 with Dinamap
- Also recorded
  - Child's state
  - Cuff size & extremity used
  - Room temperature

# Results: iron intake

	1 <sup>st</sup> trimester	2 <sup>nd</sup> trimester
Iron intake (mg)	Mean $\pm$ SD or number (%)	
Total	34 $\pm$ 17	50 $\pm$ 25
Foods only	18 $\pm$ 8	18 $\pm$ 9
Supplements only	17 $\pm$ 15	32 $\pm$ 24
Low (<27 mg/day)	364 (33%)	86 (9%)

# Results: hemoglobin

	1 <sup>st</sup> trimester	2 <sup>nd</sup> trimester
	Mean $\pm$ SD or number (%)	
Hemoglobin (g/dL)	13 $\pm$ 1	12 $\pm$ 1
Anemia*	28 (3%)	86 (9%)

\*defined as <11g/dL in 1<sup>st</sup> trimester and <10.5 g/dL in 2<sup>nd</sup> trimester (CDC)

# Results: MCV

	1 <sup>st</sup> trimester	2 <sup>nd</sup> trimester
	Mean $\pm$ SD or number (%)	
MCV (fL)	89 $\pm$ 5	91 $\pm$ 5
Microcytic*	122 (12%)	81 (8%)

\*defined as MCV <85 (MMWR 1998)

# Results: iron status & blood pressure

Blood pressure difference (mmHg) and 95% CI		
	1 <sup>st</sup> trimester	2 <sup>nd</sup> trimester
Iron intake (mg)	0.4 (0.1, 0.7)	0.0 (-0.2, 0.2)
Hemoglobin (g/dL)	0.5 (-0.2, 1.1)	0.2 (-0.5, 0.9)
MCV (10 fL)	-0.2 (-1.4, 1.0)	-0.3 (-1.4, 0.9)

Estimates adjusted for child and maternal factors.

# Results: low iron intake, anemia, microcytosis

Blood pressure difference (mmHg) and 95% CI		
	1 <sup>st</sup> trimester	2 <sup>nd</sup> trimester
Low iron intake (mg)	0.5 (-0.6, 1.7)	-0.6 (-2.3, 1.1)
Anemia (g/dL)	-1.6 (-5.0, 1.8)	0.3 (-1.7, 2.3)

Estimates adjusted for child and maternal factors.

# Results: summary

- Neither lower maternal iron intake, hemoglobin, nor MCV levels was associated with offspring BP
  - CI's exclude clinically important effects in hypothesized direction

# Context

- 3 studies with consistent results

Author / Year	n	Trimester	Result
Bergel 2000	518	3rd	Lower hemoglobin → 1.3 mmHg <i>lower</i> BP
Whincup 1994	1311	?	No association of hemoglobin or MCV
Brion 2008	7484	1 <sup>st</sup> & 3 <sup>rd</sup>	No association of iron intake or anemia

# Context

- 2 studies with contrasting results
- Small (Godfrey)
- No control for confounding (Law)

Author / Year	n	Trimester	Result
Godfrey 1994	77	1 <sup>st</sup>	Lower hemoglobin à 2.6 mmHg higher BP
Law 1991	405	?	Anemia à 2.9 mmHg higher BP

# Strengths and limitations

- Large cohort with prospective measures in pregnancy
  - 1<sup>st</sup> and 2<sup>nd</sup> trimester
  - No 3<sup>rd</sup> trimester data
- Detailed assessment of potential confounders

# Strengths and limitations

- Anemia rare
  - No association even at lowest Hgb levels
- Blood pressure measured carefully
  - Tracking from preschool to adulthood
  - Latent effects?
- Examined iron intake and hematologic measures
  - Ferritin and other markers of iron status not available clinically

# Implications

- In contrast to relevant animal models, in developed countries maternal iron status in pregnancy does *not* appear to influence offspring blood pressure

# Acknowledgements

- Matthew Gillman (PI of Project Viva)
- Co-authors
  - Sheryl Rifas-Shiman
  - Janet Rich-Edwards
  - Ken Kleinman
  - Emily Oken