Preconception and Multigenerational Health: Links Between Cardiovascular and Reproductive Health

Thursday May 2nd, 11.30-1pm CT

A webinar with Dr. Emily Harville, PhD

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harville@tulane.edu
<table>
<thead>
<tr>
<th>Webinar objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>List</strong></td>
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<tr>
<td><strong>Assess</strong></td>
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<tr>
<td><strong>Discuss</strong></td>
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</tbody>
</table>
Reproductive and cardiovascular health are linked

- Poorer health at birth
  - Low birthweight
  - Reduced fetal growth

- Poorer cardiovascular health
  - Preconception hypertension
  - Preconception diabetes

- Poorer health during pregnancy
  - Gestational hypertension
  - Gestational diabetes
  - Pre eclampsia

- Poorer health later in life
  - Diabetes
  - Hypertension
  - Cardiovascular disease
Cardiovascular and reproductive health are linked

- Poorer health at birth
- Poorer cardiovascular health
- Poorer health during pregnancy
- Poorer health later in life

Generation 1

Generation 2

Poorer health at birth
Poorer cardiovascular health
Cardiovascular health and reproductive health across generations
Transgenerational effects?
Poorer health at birth → cardiovascular health prior to pregnancy

**Poorer health at birth**
- Low birthweight
- Reduced fetal growth

**Poorer cardiovascular health**
- Preconception hypertension
- Preconception diabetes

**Poorer health during pregnancy**
- Gestational hypertension
- Gestational diabetes
- Pre-eclampsia

**Poorer health later in life**
- Diabetes
- Hypertension
- Cardiovascular disease
Low birthweight and cardiovascular health in adolescence and adulthood

Birthweight <1 kg
Mean GA 27.1 weeks
Mean age 31.8

Meta-analysis of the difference in systolic blood pressure (SBP) between participants born preterm or very low birth weight (VLBW) vs term. B, adjusted for SES, C, adjusted for height/weight/BMI

Mean age at BP measurement: 17.8

2.2 mm Hg (95% CI: 1.1-3.3 mm Hg) higher for preterm or VLBW versus term participants. Most-adjusted: 2.5 mm Hg (95% CI: 1.7-3.3 mm Hg). Higher-quality 3.8 mm Hg (95% CI: 2.6-5.0 mm Hg)
Prevalence of hypertension, obesity, metabolic syndrome, and fatty liver index greater than 30 in adults who were born early preterm or late preterm compared with adults born at term (controls), Northern Finland, 2009–2011.
Developmental Origins of Health and Disease

Potential Mechanisms
- Alterations in the maternal/fetal endocrine milieu
- Placental defects
- IUGR/compensatory growth
- Epigenetic regulation
- Oxidative stress/inflammation

Physiological Adaptations
- Reproductive System
  - Altered reproductive neuroendocrine function
  - Ovarian defects
  - Advanced/delayed puberty
  - Oligo-ovulation
  - Reduced fertility
- Metabolic System
  - Glucose intolerance
  - Insulin resistance
  - Hyperinsulinemia
  - Dyslipidemia
  - Leptin resistance
  - Obesity
- Cardiovascular System
  - Hypertension
  - Coronary heart disease
  - Stroke
  - Atherosclerosis
- Other Systems
  - Reduced cognitive function
  - Altered behavior
  - Increased risk of cancers
  - Premature aging

From: Developmental Programming, a Pathway to Disease
Endocrinology | Copyright © 2016 by the Endocrine Society
Cardiovascular health prior to pregnancy → poorer health during pregnancy

Poorest health at birth
- Low birthweight
- Reduced fetal growth

Poorest cardiovascular health
- Preconception hypertension
- Preconception diabetes

Poorest health during pregnancy
- Gestational hypertension
- Gestational diabetes
- Pre-eclampsia

Poorest health later in life
- Diabetes
- Hypertension
- Cardiovascular disease
Preconception health

Typical levels of preconception exposures for young women in high-income countries (solid lines) and hypothesized optimal exposures before conception (dashed lines), with lack of evidence on exposure trajectories (grey area); adapted from Lancet 2018 Preconception health.¹
Forest plot of studies of superimposed pre-eclampsia in women with chronic hypertension stratified according to study design.

Kate Bramham et al. BMJ 2014;348:bmj.g2301
Preconception type 2 diabetes

(A) Prevalence of pre-pregnancy diabetes per 100 deliveries ...2000. (B) Prevalence of pre-pregnancy diabetes per 100 deliveries ... 2010.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Type 2 diabetes (n = 138)</th>
<th>No diabetes (n = 27 075)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGA†</td>
<td>28 (20.3)</td>
<td>2087 (7.7)</td>
<td>3.05 (1.99–4.67)</td>
<td>2.13 (1.37–3.32)</td>
</tr>
<tr>
<td>SGA†</td>
<td>22 (15.9)</td>
<td>3964 (14.7)</td>
<td>1.10 (0.70–1.74)</td>
<td>1.38 (0.87–2.20)</td>
</tr>
<tr>
<td>IOL‡</td>
<td>74 (53.6)</td>
<td>5738 (21.2)</td>
<td>4.30 (3.04–6.08)</td>
<td>4.03 (2.71–5.99)</td>
</tr>
<tr>
<td>Caesarean section‡</td>
<td>74 (53.6)</td>
<td>7116 (26.3)</td>
<td>3.24 (2.28–4.62)</td>
<td>2.10 (1.44–3.06)</td>
</tr>
<tr>
<td>Preterm birth§</td>
<td>31 (22.5)</td>
<td>2186 (8.1)</td>
<td>3.30 (2.16–5.04)</td>
<td>2.74 (1.78–4.24)</td>
</tr>
<tr>
<td>Gestational hypertension§,‡‡</td>
<td>7 (5.1)</td>
<td>527 (2.0)</td>
<td>2.69 (1.26–5.77)</td>
<td>1.58 (0.73–3.43)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>12 (8.7)</td>
<td>645 (2.4)</td>
<td>3.90 (2.15–7.08)</td>
<td>2.75 (1.49–5.10)</td>
</tr>
<tr>
<td>SCN‡‡</td>
<td>98 (78.4)</td>
<td>4142 (15.9)</td>
<td>19.21 (12.50–29.52)</td>
<td>19.34 (12.37–30.25)</td>
</tr>
<tr>
<td>NICU‡‡</td>
<td>10 (7.4)</td>
<td>727 (2.7)</td>
<td>2.87 (1.50–5.47)</td>
<td>1.94 (0.94–4.01)</td>
</tr>
<tr>
<td>Hydropygaemia§,‡‡</td>
<td>31 (22.5)</td>
<td>1074 (4.0)</td>
<td>7.01 (4.66–10.56)</td>
<td>4.90 (2.79–8.01)</td>
</tr>
<tr>
<td>Jaundice‡</td>
<td>28 (20.3)</td>
<td>1737 (6.4)</td>
<td>3.71 (2.45–5.64)</td>
<td>2.58 (1.61–4.13)</td>
</tr>
<tr>
<td>Respiratory distress‡,‡</td>
<td>10 (7.3)</td>
<td>1039 (3.8)</td>
<td>1.96 (1.03–3.71)</td>
<td>0.78 (0.38–1.50)</td>
</tr>
<tr>
<td>Shoulder dystocia§§</td>
<td>5/64 (7.8)</td>
<td>498/19 958 (2.5)</td>
<td>3.31 (3.64–18.91)</td>
<td>2.72 (1.09–5.78)</td>
</tr>
<tr>
<td>Apgar &lt; 7 at five minutes‡,§§</td>
<td>5/64 (7.8)</td>
<td>577/19 887 (2.9)</td>
<td>2.83 (1.73–5.12)</td>
<td>0.91 (0.38–2.20)</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>6 (4.4)</td>
<td>996 (3.7)</td>
<td>1.19 (0.52–2.71)</td>
<td>1.00 (0.69–1.01)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>3 (2.2)</td>
<td>394 (1.5)</td>
<td>1.50 (0.48–4.75)</td>
<td>1.40 (0.44–4.46)</td>
</tr>
</tbody>
</table>

Data are presented as count (proportion), crude and adjusted odds ratios (OR) and 95% confidence interval (CI).

All outcomes are adjusted for age and BMI category (normal < 25 kg/m², overweight 25–29.9 kg/m², obese ≥ 30 kg/m²). Additional adjustments:
- †Parity, smoking, country of birth.
- ‡Parity, smoking, pre-eclampsia.
- §Smoking, country of birth, pre-eclampsia.
- ¶Parity.
- **Smoking, country of birth.
- #§Gestation at birth.
- #§§Apgar score < 7 at five minutes and shoulder dystocia are reported for vaginal delivery only. There was an interaction between the presence of T2D and gestational age on risk of hypoglycaemia: if born at term (8.61 [5.23–14.16]; if born preterm (1.56 [0.68–3.64]).

Treatment effects

Blood pressure control in hypertension
- Preconception care offers the option of lifestyle counseling and comorbidity and end-organ assessment
- Ideally hypertension should be controlled before conception to avoid severe hypertension
  - May be concerns about medication side effects
  - Severe hypertension should be avoided but tight control does not necessarily improve outcomes

Glycemic control in diabetes
- Preconception care reduces the risk of
  - Congenital anomalies
  - Perinatal mortality
  - Preterm delivery
Non-clinical preconception cardiovascular health

<table>
<thead>
<tr>
<th></th>
<th>Gestational Diabetes</th>
<th></th>
<th>Pre-eclampsia</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.51</td>
<td>(1.01, 2.25)</td>
<td>1.52</td>
<td>(0.87-2.66)</td>
</tr>
<tr>
<td>LDL-c</td>
<td>1.44</td>
<td>(1.00, 2.07)</td>
<td>1.22</td>
<td>(0.65-2.30)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.68</td>
<td>(1.25, 2.25)</td>
<td>1.70</td>
<td>(1.08-2.65)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.06</td>
<td>(0.75, 1.50)</td>
<td>1.28</td>
<td>(0.71-2.29)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.12</td>
<td>(0.81, 1.55)</td>
<td>0.64</td>
<td>(0.22-1.87)</td>
</tr>
</tbody>
</table>

Cardiovascular Risk in Young Finns
Outcome rates in patients with triglyceride level above and below 150 mg/dL.

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0139164
Physical fitness and GDM

Whitaker et al., 2018
Subclinical risk factors and birth outcomes

Associations of Prepregnancy Cardiovascular Risk Factors with the Offspring’s Birth Weight

Pål R. Romundstad¹, George Davey Smith², Tom I. L. Nilsen¹, and Lars J. Vatten¹

¹ Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway.
² Department of Social Medicine, University of Bristol, Bristol, United Kingdom.

Received for publication May 22, 2007; accepted for publication August 22, 2007.

Low birth weight of offspring has been associated with increased risk of maternal cardiovascular mortality, and cardiovascular risk factors measured within pregnancy have been related to offspring birth weight. It is not clear whether cardiovascular risk factors assessed prior to pregnancy are associated with the offspring’s birth weight. The authors combined baseline data from 3,461 women in the HUNT Study (1995–1997) and data on deliveries from the Medical Birth Registry of Norway up to 2005. They used linear regression to prospectively study associations between diastolic and systolic blood pressures, concentrations of triglycerides, serum total cholesterol, and high density lipoprotein cholesterol measured before conception and birth weight for gestational age of the offspring. Blood pressure measured before pregnancy was inversely associated with birth weight for gestational age, whereas unfavorable levels of serum total cholesterol, high density lipoprotein cholesterol, triglycerides, and glucose were positively associated with birth weight for gestational age. Thus, women with relatively high blood pressure tend to deliver small babies, whereas women with unfavorable lipid levels tend to give birth to large babies, suggesting reduced glucose tolerance. These findings suggest that low as well as high birth weight of the offspring may indicate increased cardiovascular risk for the mother.
## Preconception Cardiovascular Health

<table>
<thead>
<tr>
<th>Table 2: Odds Ratios for Quartiles of Plasma Lipids According to PTB Status; Referent Are Women with Term Births (n = 792)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prepregnancy Lipid Concentration</strong></td>
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<tr>
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<tr>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Quartile 4 (196–318)</td>
</tr>
<tr>
<td>Quartile 3 (173–195)</td>
</tr>
<tr>
<td>Quartile 2 (156–172)</td>
</tr>
<tr>
<td>Quartile 1 (134–155)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Quartile 4 (78–318)</td>
</tr>
<tr>
<td>Quartile 3 (58–77)</td>
</tr>
<tr>
<td>Quartile 2 (44–57)</td>
</tr>
<tr>
<td>Quartile 1 (16–43)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
</tr>
<tr>
<td>Quartile 4 (64–116)</td>
</tr>
<tr>
<td>Quartile 3 (55–63)</td>
</tr>
<tr>
<td>Quartile 2 (47–54)</td>
</tr>
<tr>
<td>Quartile 1 (25–46)</td>
</tr>
</tbody>
</table>

*Adjusted for race, parity, BMI, physical activity at baseline, age at selected birth, ever gestational hypertension or preeclampsia during follow-up, time interval from baseline measurement to selected birth.
## Time relative to pregnancy

<table>
<thead>
<tr>
<th></th>
<th>PTB RR (95% CI)</th>
<th>LBW RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>1.28 (1.05-1.57)</td>
<td>1.31 (0.97-1.76)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.19 (0.94-1.53)</td>
<td>1.14 (0.80-1.63)</td>
</tr>
</tbody>
</table>

*Cardiovascular Risk in Young Finns Study*

Harville et al, 2011
Pregnancy is also a window to later-life health

- Poorer health at birth
  - Low birthweight
  - Reduced fetal growth

- Poorer cardiovascular health
  - Preconception hypertension
  - Preconception diabetes

- Poorer health during pregnancy
  - Gestational hypertension
  - Gestational diabetes
  - Pre eclampsia

- Poorer health later in life
  - Diabetes
  - Hypertension
  - Cardiovascular disease
Pregnancy as a window to future health

Association Between a History of Hypertensive Disorder of Pregnancy or Gestational Diabetes Mellitus and Diagnosis of Hypertension and Hypercholesterolemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Model I</th>
<th>Model II</th>
<th>Model III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive disorder of pregnancy (n=2935)</td>
<td>2.04 (1.91-2.18)</td>
<td>2.12 (1.97-2.27)</td>
<td>2.12 (1.98-2.28)</td>
</tr>
<tr>
<td>Hypertension (n=367)</td>
<td>1.01 (0.94-1.08)</td>
<td>1.05 (0.97-1.12)</td>
<td>1.00 (0.93-1.08)</td>
</tr>
<tr>
<td>Hypercholesterolemia (n=308)</td>
<td>0.87 (0.69-1.09)</td>
<td>0.91 (0.73-1.14)</td>
<td>0.83 (0.66-1.05)</td>
</tr>
<tr>
<td>Gestational diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (n=367)</td>
<td>0.92 (0.75-1.15)</td>
<td>1.04 (0.83-1.31)</td>
<td>1.05 (0.84-1.32)</td>
</tr>
<tr>
<td>Hypercholesterolemia (n=308)</td>
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</table>

Results obtained with multivariable logistic regression models and expressed as odds ratios with corresponding 95% confidence intervals. Model I: adjustment for cohort and gestational diabetes mellitus (only for hypertensive disorder of pregnancy outcomes) or hypertensive disorder of pregnancy (only for gestational diabetes mellitus outcomes). Model II: additional adjustment for age, BMI, current smoking, and current alcohol consumption at study enrollment. Model III: additional adjustment for history of myocardial infarction and stroke, prevalent diabetes mellitus, total cholesterol/HDL ratio (only for hypertension outcome), and hypertension (only for hypercholesterolemia outcome) at study enrollment. BMI indicates body mass index; and HDL, high-density lipoprotein.

22,265 ever-pregnant women from the European Prospective Investigation into Cancer and Nutrition-NL study, aged 20 to 70 years at baseline (mean age 51-55)

Earlier Age of Onset of Chronic Hypertension and Type 2 Diabetes Mellitus After a Hypertensive Disorder of Pregnancy or Gestational Diabetes Mellitus, Heida, Karst; Franx, Arie; van Rijn, Bas; Eijkemans, Marinus; Boer, Jolanda; Verschuren, Monique; Oudijk, Martijn; Bots, Michiel; van der Schouw, Yvonne

Hypertension. 66(6):1116-1122, December 2015.
DOI: 10.1161/HYPERTENSIONAHA.115.06005
Women with a history of HDP were diagnosed with hypertension 7.7 years earlier since first pregnancy (95% CI 6.9-8.5) without such history.

Women with GDM were diagnosed with T2D 7.7 years earlier (95% CI 5.8-9.6) than women without such history.
92,368.6 Swedish women, 1983-2005
Experiencing multiple pregnancy complications is associated with a greater risk of cardiovascular disease, beyond single complications.

Cardiovascular and reproductive health are linked

Generation 1
- Poorer health at birth
- Poorer cardiovascular health
- Poorer health during pregnancy
- Poorer health later in life

Generation 2
- Poorer health at birth
- Poorer cardiovascular health
Offspring of hypertensive pregnancies

Offspring of hypertensive pregnancies

Followed to age ~65-75

Offspring of gestational diabetes pregnancies

Adverse perinatal and cardiovascular outcomes take a particularly hard toll on vulnerable communities.
Racial disparities

Generation 1: Poorer health at birth

- Poorer cardiovascular health
- Poorer health during pregnancy
- Poorer health later in life

Birth outcomes:

March of Dimes
Racial disparities

Poorer health at birth → Poorer cardiovascular health → Poorer health during pregnancy → Poorer health later in life

Preconception health

- Hypertension (%)
- Diabetes (%)
- Comorbid hypertension and diabetes

- Black
- White

- Generation 1

MMWR
Racial disparities

Generation 1

Poorer health at birth → Poorer cardiovascular health → Poorer health during pregnancy → Poorer health later in life

Pregnancy complications

0 1 2 3 4 5 6 7 8

gestational hypertension gestational diabetes pre-eclampsia eclampsia severe maternal morbidity (/1000)

black white

National Inpatient Sample, AHRQ, CA birth certificates, national birth cohort data
Racial disparities

Generation 1

Poorer health at birth

Poorer cardiovascular health

Poorer health during pregnancy

Poorer health later in life

Cardiovascular disease

- Diabetes
- Hypertension
- Kidney disease

CDC, NIDDK
Racial differences - The Bogalusa Heart Study

Low birthweight

- SBP
- DBP

1.43
0.98
1.00
0.83

Preterm birth

- SBP
- DBP

1.18
1.09
1.21
1.21

white
black

adjusted for cigarettes, Kotelchuck index, maternal education, parity, mother's age at child's birth, year of birth, BMI at last screening, and time (in years) between screening and birth

Harville et al., 2018
Crude incidence rates (95% CIs) of the metabolic syndrome during 20 years of follow-up for lactation categories by GDM status (1986–2006) and race (black and white).

<table>
<thead>
<tr>
<th>Race</th>
<th>Non-GDM</th>
<th>GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duration of Lactation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-1 month</td>
<td>&gt;1 months</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>Person-yrs</td>
<td>1667</td>
<td>1699</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Person-yrs</td>
<td>860</td>
<td>4,727</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>40</td>
<td>57</td>
</tr>
<tr>
<td>Person-yrs</td>
<td>2,527</td>
<td>6,426</td>
</tr>
</tbody>
</table>

Erica P. Gunderson et al. Diabetes 2010;59:495-504
Transgenerational effects
Why transgenerational effects?
Traditional genetic mechanisms explain only a small proportion of the familial clustering of obesity and cardiovascular disease.
“The CAD loci with the strongest genetic effects, such as SLC22A3-LPAL2-LPA and chromosome 9p21, still only confer a 20–37% increased risk and the vast majority of the loci modulate risk by 10% or less. Furthermore, the ~60 loci for CAD collectively explain <20% of the heritability, raising the question of where to search for the remaining genetic risk.”

Genetics of cardiovascular disease

- Non-diabetic kidney disease - explained by genetic variants in apolipoprotein 1 (APOL1) gene
  - More common in SSAA; confers immunity against trypanosomiasis

- No convincing genetic variant linked with hypertension excess
Birthweight distributions of 3 Illinois subpopulations

Things that are not the cause of disparities

Poverty, education

Smoking
Reproductive outcomes

Percentage small-for-gestational-age\textsuperscript{a} by maternal risk status and race; 1990-91 single live births, 34-42 weeks' gestation, to US-resident mothers

\begin{tabular}{|l|c|c|}
\hline
 & ELR & Total \\
\hline
African-American: % SGA\textsuperscript{a} & 8.24 & 15.85 \\
[95\% CI] & [7.89, 8.61] & [15.76, 15.94] \\
\hline
White: % SGA\textsuperscript{a} & 3.29 & 8.03 \\
[95\% CI] & [3.23, 3.35] & [8.00, 8.06] \\
\hline
African-American/White SGA\textsuperscript{a} risk ratio & 2.64 & 2.16 \\
\hline
\end{tabular}

\textsuperscript{a}Small for gestational age (SGA) defined as less than the 10th percentile of birthweight for gestational age from the 1991 US Reference Curve. ELR, extremely low risk group; CI, confidence interval.

Hypertension

**Figure 1** Interaction plots of self-identified race and education: US Family Blood Pressure Program, 1996-2000.

Note: AA = African American; SBP = systolic blood pressure. Interaction plots of education × self-identified race, with education divided into less than or equal to a high school degree, or greater than a high school degree (a), and separated by gender (b). SBP measures are adjusted for covariates of age, gender, age × gender, and body mass index (defined as weight in kilograms divided by the square of height in meters).
Smoking

Figure 1. Cigarette Smoking Before and During Pregnancy, by Maternal Race/Ethnicity, 2011*

*Includes data from 23 states (AR, CO, GA, HI, ME, MD, MI, MN, MO, NE, NJ, NM, NY, OK, OR, PA, RI, UT, VT, WA, WV, WI, WY) and New York City. Mothers completed surveys between 2 and 9 months postpartum. Multiple race data were not reported by 5 of 23 states (AR, HI, ME, NJ, WV); therefore, specific race categories may include multiple race mothers. **Defined as the proportion of mothers who reported smoking in the 3 months before pregnancy. *Defined as the proportion of mothers who reported smoking in the last 3 months of pregnancy.

Transgenerational effects?
Transgenerational effects

A woman who smokes while pregnant induces epigenetic changes in three generations at once: in herself, her unborn daughter, and her daughter’s reproductive cells.

https://www.harvardmagazine.com/2017/05/is-epigenetics-inherited
Epigenetics

Epigenetic mechanisms are affected by these factors and processes:

- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

Health endpoints:

- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

DNA methylation:
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histone modification:
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.
Animal studies

Generation 1 GDM

Generation 1 low protein diet

Generation 1 nutritionally deprived

Generation 2 impaired glucose tolerance

Generation 2 growth retardation

Generation 3 increased birthweight

Generation 3 changes in glucose and insulin metabolism, even when embryo transferred

Generation 3 higher trunk diameter, fat, lipids

mice

rats

rats

swine
Human studies

- Generation 1 changes in food supply early in life
- Generation 1 diabetes mortality
- Generation 1 cardiovascular mortality
- Generation 1 famine
- Generation 2 hyperglycemia
- Generation 3 U-shaped or lower birthweight
- Generation 3 increased mortality in grandsons
- Generation 3 lower birthweight
- Generation 3 increased CVD mortality

Historical records, Sweden

Records, Norway

Records, Norway

China
Human studies

- **Bogalusa Heart Study**
  - Generation 1: BMI, glucose, triglycerides
  - Generation 2
  - Generation 3: birthweight

- **Malta, clinical records**
  - Generation 1: BMI, metabolic syndrome
  - Generation 2
  - Generation 3: no difference in birthweight
Human studies

Generation 1 grandmaternal smoking

Generation 2

Generation 3 birthweight and length increased

ALSPAC

Generation 1 grandmaternal smoking

Generation 2 nonsmoking mothers

Generation 3 higher birthweight/greater obesity

Nurses’ Health
Epigenetics may contribute to the embodiment of racial disparities

- Epigenetic differences are associated with CVD
- Stress during pregnancy has been associated with changes in methylation in the next generation

Kuzawa, 2009
Problems with studying transgenerational health

- Difficult to set up – long time frame or reliance on existing records, which may not have the necessary information
- Privacy/confidentiality for accessing data
- Quality of linkage across generations
- Difficulty of complete follow-up, especially through the male line
- Observed patterns may be consistent with many hypotheses
- Difficulty of testing hypotheses and confounder control, particularly for second-generation
- Missing data
- Fertility/socially patterned reproduction
## Future directions - Transgenerational health

<table>
<thead>
<tr>
<th>Expand</th>
<th>Include</th>
<th>Examine</th>
<th>Take advantage</th>
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<tbody>
<tr>
<td>Expand existing prospective cohorts, pregnancy, and child health studies</td>
<td>Include biological markers and test mechanisms</td>
<td>Examine mediation and pathway analyses</td>
<td>Take advantage of natural experiments and discrepant generations</td>
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How can we use these to improve women’s health?

• Recognize that health is linked across the life course and across generations
How can we use these to improve women’s health?

- Good health during pregnancy starts with good family planning.
How can we use these to improve women’s health?

Making the case for preconception care, Public Health England
How can we use these to improve women’s health?

Follow-up for women who experience pregnancy complications

- Postpartum is a time when care continuum can fail
- Pediatricians treat children
- Obstetricians treat pregnant women
- PCPs may not ask about pregnancy history
Clinical care solutions

- Integrated and functioning EMR systems to establish flagging tools for certain conditions (e.g., GDM)
- Empower women to share their birth narratives
- Training on hand-off of care in medical/midwife/RN/PA students to know the right questions to ask or to identify when information is missing, especially for women of reproductive age
- Improve predictive analytics to identify women who are likely to progress to cardiovascular disease
- Expand payment models to bundle postpartum services with delivery and have a “well-mom” schedule parallel with well-baby
How could a life course/DOHaD perspective inform policy?

Goodman et al., Analyzing policy through a DOHaD Lens

- **Paid family leave**
  - May decrease stress among pregnant women either through offering an opportunity to stop working during pregnancy (antenatal leave) or through the anticipation of paid postpartum leave and this may result in more appropriate birthweight and decreased PTB.
  - Appropriate birthweight is an indicator of fetal developmental processes that contribute to the long-term development of coronary heart disease, diabetes mellitus, and other conditions, thus amplifying the potential impact of PFL.
  - The influence of PFL may be further amplified through its well-established connection to breastfeeding, providing a link to later life obesity and cardiometabolic disease through healthier infant weight gain.

- **Sugar sweetened beverage taxes**
  - SSBS were the largest single dietary sources of energy consumed in pregnancy.
  - Observational evidence suggests that greater maternal SSBS consumption in pregnancy is associated with adverse birth outcomes associated with life course disease risk in the offspring, including higher risk of PTB.
  - Prenatal SSBS consumption is also associated with greater adiposity in children.
  - Applying a DOHaD lens to evaluate SSBS tax policies requires integration of pregnant women as a subgroup of interest, and extending policy simulations to consider intergenerational effects. It also requires more empirical research on the intergenerational effects of consuming SSBSs and their alternatives prior to, during, and after pregnancy, as well as consumption by fathers.

- **Housing policy**
  - Housing transitions and housing instability have been associated with increased risk of LBW among young, urban pregnant women.
  - Effects of renewal policies that result in housing transitions are differential by race/ethnicity.
    - Very high levels of gentrification were associated with increased PTB compared to non Hispanic blacks, but protective among non Hispanic whites.
  - While the housing-related literature is beginning to concern itself with effects on pregnant women, the consideration of potential health effects stops at birth and fails to take into account the long-term health trajectory that birth outcomes set in.
  - A DOHaD lens considers the positive and negative consequences of what might seemingly be economic development policies, but also the potential effects of these policies on the second generation.
Don’t blame the mothers

Careless discussion of epigenetic research on how early life affects health across generations could harm women, warn Sarah S. Richardson and colleagues.

From folk medicine to popular culture, there was a disorientating fascination with how the experiences of pregnant women exerted their effects on the developing embryo. The latest wave in this discussion flows from studies of epigenetics — analyses of heritable changes in DNA that affect gene activity but not the underlying sequence. Such DNA modifications have been implicated in a child’s future risk of obesity, diabetes and other diseases.

Findings in the press reveal how these discussions are often simplified to focus on the mother’s age. Mother’s diet during pregnancy affects a child’s DNA (BMJ). A recent Nature study reports that maternal exposure to alcohol, tobacco and other substances during pregnancy can alter her daughter’s DNA (Nature). The question about the long shadows of the maternal environment are part of a long-running debate on epigenetics and its role in disease.

For example, one study revealed that 4% of children born to women with type 2 diabetes develop diabetes by their 40th birthday, compared with 8% of children whose mothers developed diabetes after pregnancy. The study concludes that such findings could guide policies that support pregnant women and their children, but further research is needed to determine the extent to which such findings are applicable to other populations. The study also highlights the importance of ongoing research to better understand the mechanisms underlying these findings.

ALARMING PRECEDENTS

There is a long history of society blaming mothers for the ill health of their children. Prenatal care and infant health have been seen to improve once the mother is recognized as an important factor in the health of the child. The impact of prenatal care on the health of the child has been recognized for centuries, and it is now widely accepted that the health of the mother during pregnancy is crucial. It is important to note that the health of the mother during pregnancy is not just about the health of the baby, but also about the health of the mother herself.

Healthcare providers have a responsibility to ensure that women have access to the care they need during pregnancy, and that they are educated about the importance of maintaining a healthy lifestyle. This includes not only the mother’s nutrition and exercise, but also her mental health and stress levels. It is also important to ensure that women have access to prenatal care and that they are encouraged to seek help if they are experiencing any complications.

The health of the mother during pregnancy is not just important for the health of the baby, but also for the health of the mother. It is important to ensure that women have access to the care they need during pregnancy, and that they are educated about the importance of maintaining a healthy lifestyle. This includes not only the mother’s nutrition and exercise, but also her mental health and stress levels. It is also important to ensure that women have access to prenatal care and that they are encouraged to seek help if they are experiencing any complications.
All of which goes beyond clinical care

- Health insurance and access to care encourage health across the life course
- Paid maternity leave allows families to take care of themselves and their children
- Sexual responsibility among men encourages planned pregnancies
- Economic stability allows for long-range planning and prioritizing health
- Neighborhoods that are safe encourage healthy activity
- Evidence based medical care and community interventions mean programs that work

More ideas?
Goal: All babies born healthy!
All women healthy throughout life!

Questions?
Send me your baby and 4+ generation pictures!
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