Risk Factors for Congenital Heart Defects: A case study
Admission Note

- BG XXX is the 3584 gram product of a 37 WBD singleton gestation to a 22 year old G2P1A1 Caucasian female via C-section 2° to late fetal decels and FTP.
Infant characteristics

• Sex ratio
  - Males > females
  - International HLHS OR=1.7 (95% CI:1.55-1.85)

• Weight
  - BWI SGA OR= 4.4 (95% CI: 2.9-6.8)
  - NBDPS SGA OR= 2.0-3.0

• Maternal ethnicity
  - BWI, Atlanta - no differences
Maternal History

- PMHx: No diabetes, HTN
- PSHx: 2001 MVA liver lac and small intestinal injury s/p SBR
- Meds: PNV began @ 1st prenatal visit
- PObHx: G1 - SAB
Diabetes and HLHS

• Baltimore Washington Infant Study
  - Cases (4/377): Controls (23/3572)
    HLHS: OR = 1.7 (95% CI: 0.6-4.8)

• National Birth Defects Prevention Study
  - Cases (3/192): Controls (21/4086)
    • HLHS: OR = 1.8 (95% CI: 0.4-7.8)
Diabetes and Other CHDs

- Hypertrophic cardiomyopathy
- Double outlet right ventricle
- Truncus arteriosus
- Transposition of the great arteries
- VSD
Mechanism

- Hyperglycemia - Oxidative Stress
- Hyperinsulinemia
- Hypoglycemia - Lactic Acidosis
- Modifiers of diabetic embryopathy
  - Antioxidants
  - Lipids
  - Arachidonic Acid
- Genetic Variants
Maternal Medications
FDA Pregnancy Categories

• A - Controlled studies in pregnancy (<1%)
• B - Animal studies show no risk or human data are reassuring
• C - Human data lacking; animal studies positive or not done (66%)
• D - Human data show risk; benefit may outweigh
• X - Animal or human data positive; no benefit
Maternal Hypertension

- Angiotensin-converting-enzyme (ACE) inhibitors
  - Tennessee Medicaid
  - 29,507 infants 1985-2000
  - OR = 3.7 (95% CI: 1.9 - 7.3)

- 1995 - 2002 use of ACE inhibitors increased from 2.4% to 4.4%
ACE inhibitors pose risk of birth defects

Mothers who used ACE inhibitors, a blood pressure treatment, were more than twice as likely to have babies with birth defects.

### Percentage of birth defects

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>7.12%</td>
</tr>
<tr>
<td>Other blood pressure drug</td>
<td>1.73%</td>
</tr>
<tr>
<td>No blood pressure drugs</td>
<td>2.63%</td>
</tr>
</tbody>
</table>

### ACE inhibitor defects

- 50% Cardiovascular
- 33% Other
- 17% Central nervous system

SOURCE: New England Journal of Medicine
Multivitamins and Heart Defects

Conotruncal Heart Defects
- Hungary '96 (RCT)
- Atlanta 2000 (CC)

Outflow Tract Defects
- Hungary '96 (RCT)
- California '95 (CC)
- Baltimore-Washington '97 (CC)
- U.S.- Canada '99 (CC)
- Atlanta 2000 (CC)

Ventricular Septal Defects
- Hungary '96 (RCT)
- U.S.- Canada '99 (CC)
- Atlanta 2000 (CC)

All Heart Defects
- Atlanta 2000 (CC)

Odds Ratio and 95% CI

DNA Synthesis

5,10-CH₂-THF
5-CH₃-THF
B₁₂

THF

DHF

MTHFR
MTRR
TCII

TCII

MTRR

DNA Methylation

Methionine

SAM

SAH

Homocysteine

CBS

Cystathionine

Cysteine

GSH

SAM

Antioxidant Defense

Folic Acid Pathway

Folic Acid Pathway

Antioxidant Defense
N=654

N=317

N=337

GSSG:GSH >0.43

Yes

Meth >21.6µM

No Yes

N=122

N=195

N=212

N=125

Hcy>9.5µM

No Yes

N=61

N=61

N=114

N=81

N=118

N=94

OR=16.4

OR=6.1

OR=1

OR=4.0

OR=7.1

OR=40.1

OR=198.2

OR=40.1
Gaps identified by Botto AJMG 2003

• Do multivitamins reduce the risk?
• How much do they reduce the risk?
• What is the magnitude of effect?
• What components of multivitamins account for effect?
• What components of multivitamins account for effect?
• What dose is most effective?
• What is the mechanism?
• Do gene-environment interactions play a role?
Admission Note

• SocHx: Denies smoking, drug use
• Occassional alcohol use during 1\textsuperscript{st} trimester
• Family Hx: noncontributory
Maternal smoking

- BWI – nonsignificant OR

- NBDPS – nonsignificant OR
Alcohol Use

- 77.6% ever use alcohol
- 58.8% drink while pregnant

- Conotruncal heart defects
  - California Birth Defect Monitoring Program
  - ≤ 1X week OR = 1.3 (95% CI: 1.0, 1.9)
  - ≥ 1 week OR = 1.9 (95% CI: 1.0, 3.4)
FAS Facial Characteristics

- epicanthal folds
- small eye openings
- flat midface
- upturned nose
- smooth philtrum
- thin upper lip

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Family History

- **BWI**
  - OR = 4.8
  - 95% CI: 2.1 - 10.8
Maternal prenatal labs

• HIV/RPR/Hep B – negative
• Rubella – immune
Congenital Rubella Syndrome
Rubella Immune

- Rubella vaccination introduced in US 1969
- 91% of US women seropositive for rubella
- 75% of Sri Lankan women positive for rubella IgG
Admission Note

• PE: General Appearance - term newborn, mild respiratory distress, minimal central cyanosis initially, no obvious congenital malformations
Down Syndrome

- Chromosome 21
- 50%
- Why??
Causes of Common Pediatric Conditions

Genetic Factors

- Cystic Fibrosis
- PKU

Environmental Factors

- Birth Defects
- Asthma
- Prematurity
- Trauma
- Child Abuse

Multifactorial
Combined effect of homocysteine, smoking and MTHFR 677C>T genotype on CHD risk
HapMap Project

- International endeavor
  - Canada, China, Japan, Nigeria, United Kingdom and United States
  - Total of 270 individuals to be analyzed for 1 million SNPs
- Purpose
  - Provide a map of SNPs that will allow scientists to find and test susceptibility loci
  - Provide representative, genomewide haplotypes from different populations
  - Initial phase completed ahead of schedule
  - Publicly available data for 4 different populations
Birth Defects Research and Prevention

Research

Evaluation

Prevention

Take Action
Why is Preconception Care a public health concern?
Preconception Care

• Risk assessment

• Health Promotion

• Intervention
Our Vision of Preconceptional Care

- Determine genetic susceptibilities: genome-wide association studies
- Establish genetic and metabolic high-risk profile
- Provide diagnostic tools for physicians
- Design targeted treatments
- The benefits will be widespread and many cannot even be predicted yet
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