Prenatal Factors and Pregnancy Outcomes: Role of the Pediatrician

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Faculty Disclosure

In compliance with ACCME Guidelines, I hereby declare:

• I do not have financial or other relationships with the manufacturer(s) of any commercial services(s) discussed in this educational activity.
Infant Mortality in the USA in 2015

- Birth defects
  - 1 in every 33 babies born each year.
- Prematurity and/or low birth weight
  - 1 of every 10 infants born in 2015
- Maternal complications of pregnancy
  - Acute, e.g. infections, or chronic e.g. diabetes
A growing income gap in infant mortality

Cumulative probability of infant death per 1,000 live births, by infant age, in U.S.

- Disadvantaged mothers
- Wealthy mothers

Source: Alice Chen, Emily Oster and Heidi Williams
Developmental Disabilities

Causes:
- **Prenatal**
  - Genetic
  - Chromosomal
  - Non Chromosomal Syndrome
  - Congenital Anomalies
  - Chemical Insults, e.g. FAS
  - Intrauterine Infections
  - Placental Insufficiency
  - Maternal Illness
  - Poor Antenatal Care
- **Perinatal**
  - Prematurity
  - Respiratory Distress Syndrome
  - Cardiovascular instability
  - Hypoxic-Ischemic injury
  - Cerebral Hemorrhage
  - High levels of Oxygen
  - Jaundice
  - Infections
- **Postnatal**
  - Medical Complications
  - Inadequate Intervention
  - Environmental Factors
  - Poverty
  - Neglect & Abuse

Central Nervous System

Functional Domain:
- **Motor**
- **Cognitive**
- **Behavioral**

Consequences:
- **Mild:** Dysooordination
- **Severe:** Cerebral Palsy
- **Learning Disabilities**
- **Intellectual Disabilities**
- **ADHD**
- **Autism/PDD**
CASE PRESENTATION

A CASE OVERVIEW

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CHIEF COMPLAINT

- 2Y 1M male born at 24.3GA presenting with developmental delay
- Brought by Maternal Grandmother
CURRENT STATUS

- MGM states patient has history of delayed language and poor “control of lower limbs”
- Cruises, not yet walking
- Not picking up objects using thumb and forefinger
- Uses about 5 words, no phrases
- Difficulty chewing
- Does not follow directions
BIRTH HISTORY

• 24.3GA emergency C/Section
  – maternal eclampsia
  – Apgars 5, 7
• Maternal HIV+,  
  – zidovudine prior to delivery 
  – DNA PCR negative x 3
• NBS: low T4
  – TFT: elevated TSH, low FT4
  – Started on levothyroxine DOL 29
• NICU x 4 months
  – CPAP 8 weeks → intubation x 2 weeks → CPAP x 4 weeks → RA DOL 115
  – pRBC transfusion x 7 (AOP)
MEDICAL HISTORY

- Small muscular ASD
  - followed by Cardiology
- Grade IV IVH w/ PVL
  - followed by Neurology
- ROP Stage 2 Zone 2
  - followed by Ophthalmology
- Congenital Hypothyroidism
  - followed by Endocrinology
- Prematurity
  - followed by Developmental Progress Clinic
FAMILY & SOCIAL HISTORY

• Family History
  – ADHD – sister
  – HIV – mother
  – SLE – MGM
  – Father’s medical history unknown

• Social History
  – Lives with mom and 2 older siblings
  – Father is not available
DEVELOPMENTAL HISTORY

- 4 mo – lift head up, focus on face, startle with noise
- 7 mo (3 mo) – roll over prone to supine
- 8 mo (4 mo) – sit up with assistance
- 10 mo (6 mo) – babbling, smile reciprocally, sitting independently
- 18 mo (14 mo) – 1 word, crawling, pull to stand
- 24 mo – 5 words, cruising, attempts standing without support but falls within seconds
• OBSERVATIONS
  – crawling, cruising along chairs, tries 2 steps w/fall,
  – not interactive with MGM, smiles inconsistently, babbles

• GENERAL
  – Responsive, reaches for examiner’s stethoscope

• NEURO
  – 2+ and symmetric reflexes UE and LE;
  – increased spasticity at ankle > knee; no ankle clonus

• GAIT
  – wide stance when assisted walking
  – Has AFO’s
TREATMENTS TO DATE

• Babies Can’t Wait
  – PT – 1x/week
  – No OT
  – No ST

• Bilateral Ankle-Foot Orthoses
• Walker
ASSESSMENT AND PLAN

• 25 month-old ex-premature boy with history of maternal HIV+, Grade IV IVH, and congenital hypothyroidism,

• Diagnosis: Cerebral Palsy, Spastic Diplegic Type with Developmental/Cognitive and Speech delay

• Recommendations:
  – PT
  – OT
  – ST
  – Aquatic Therapy
  – Walker
  – Nutritional Support
  – Social Support for Family
  – Prepare for Special Needs Preschool when he turns 3 years old
Lessons from this patient:

- Maternal Health and Intrauterine Environment
  - HIV and Medications
  - Preeclampsia
  - Stress
- Genetic factors
  - MGM with SLE
  - Sister with ADHD
- Social Determinants of Health
  - Single mother
  - African American
- Prematurity
  - Adverse developmental outcomes with Spastic Diplegic CP
Prematurity and Cerebral Palsy

• In a recent report from Sweden, the prevalence of cerebral palsy was as follows:
  – 1.1/1000 live births for children born full term
  – 6.7/1000 live births for children born at 32 to 36 weeks of gestation
  – 40.4/1000 live births for children born at 28 to 31 weeks of gestation
  – 76.6/1000 live births for children born before 28 weeks of gestation

• There was a similar stepwise increase when prevalence of cerebral palsy was calculated by birth weight category:
  – 1.2/1000 live births for birth weight above 2500 g
  – 6.7/1000 for birth weight of 1500 to 2500 g
  – 54/1000 for birth weight of 1000 to 1499 g
  – 82/1000 for birth weight below 1000 g
Preterm Infants at risk after 10 Years

- High Prevalence of Learning Disabilities, ADHD, Poor Academic Performance and Social Functioning

- Pre-term and low birth weight infants who do not suffer from cerebral palsy are still at risk for subtle developmental delays that are more social, behavioral and cognitive in nature that are often undetected until a child reaches school age.

Barlow & Lewandowski, et al Syracuse University & Crouse-Irving Memorial Hospital
Preterm Infants at risk after 10 Years

• The prevalence of school problems with pre-term children warrants greater attention from school professionals.

• Interventions should be implemented for all pre-terms as early as possible to halt or prevent future problems and closely monitor their social, behavioral and academic progress.

Barlow & Lewandowski, et al Syracuse University & Crouse-Irving Memorial Hospital
Prematurity and ADHD

Too Young or Too Small

Premature birth and low birth weight are risk factors for later development of hyperkinetic activity disorder, say Danish researchers.

Gestational age (wks)*
- <34: 3.1
- 34-36: 1.8
- 37-39: 1.2
- 40-42: 1
- 43-44: 0.9

Birth weight at term**
- 1,500-2,499g: 2.4
- 2,500-2,999g: 1.7
- 3,000-3,999g: 1
- 4,000-5,999g: 1.0

Adjusted risk ratio

* Controls=20,100 / cases=834  ** Controls=17,625 / cases=763
Source: Karen Markussen Linnet, Ph.D., et al., Archives of Disease in Childhood, June 2006
Prematurity and Autism

- A population-based study of adults born at very low gestational age compared with term-born adults described a significant increased risk for Autism:
  - relative risk of 7.3 among those born at 28 to 30 weeks gestation
  - relative risk of nearly 10 in those born at 23 to 27 weeks gestational age

(Moster, Markestad, et al, 2008)
Autism in ex-preterm infants: Additional Risk Factors

- lower birth weight and lower gestational age
- male gender
- chorioamnionitis
- acute intrapartum hemorrhage
- illness severity on admission
- abnormal MRI studies
- 37% of infants with cerebellar injury tested positive for early signs of autism

Limperopoulos et al, Pediatrics. 2008 McGill University, Montreal, Quebec, Canada.
Consequences:

Mild:
- Dyscoordination

Severe:
- Cerebral Palsy

Functional Domain:
- Motor
- Cognitive
- Behavioral

Causes:

Prenatal - Genetic
- Chromosomal
- Non Chromosomal Syndrome
- Congenital Anomalies
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Perinatal - Respiratory Distress Syndrome
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Postnatal - Medical Complications
- Medical Illnesses
- Inadequate Intervention
- Environmental Factors
- Neglect & Abuse
Long-term Family Outcomes for Children with Very Low Birth Weights

- Families with children of birth weights less than 750 g experienced greater stress than did families of children born at term.

- Adverse family outcomes were mediated by ongoing problems in child functioning.

- Families who were socio-demographically advantaged experienced greater stress than did those who were disadvantaged.

Conclusions

- The results support the need to monitor family outcomes and develop interventions for both the child and family.

Prenatal Causes of Adverse Birth Outcomes

• Maternal Illness
  – infections, e.g. ToRCH, HIV, Diabetes
• Lifestyle
  – Nutrition, exercise & substance use
• Personal Characteristics
  – Emotional state, e.g. depression or anxiety
• Socioeconomic factors
  – Education & income
• Chronic Stress
  – Poverty, discrimination, domestic violence,
Rubella

• Between 1963 and 1965 a rubella epidemic swept the nation.
• 20,000 pregnant women who contracted the disease gave birth to infants with congenital anomalies and neurodevelopmental consequences
Congenital Rubella – Neurodevelopmental Consequences

- Intellectual Disability
- Seizure Disorder
- Blindness
- Deafness
- Autism
Zika and the Fetal Brain

- Zika virus Inhibits neural stem cell growth
- Decreased brain tissue
- Retinal pathology
- Abnormal muscle tone
- Limited limb movement
- Joint contractures
Congenital Zika Syndrome without Microcephaly at Birth

- Microcephaly from congenital infection can occur after birth.
- The full spectrum of poor outcomes caused by Zika virus infection during pregnancy remains unknown.
Fetal Alcohol Syndrome

• Alcohol and other drugs taken by the mother during pregnancy can have a deleterious effect on the growth and development of the fetus and child

• Warning labels on bottles of alcohol and education of public
Tobacco Exposure

- The effects of the toxin not only have a direct effect on the smoker and on the fetus but can have long term health implications for the rest of that child’s life.
Long-Term Consequences of Fetal and Neonatal Nicotine Exposure

- Increase rate of Prematurity, Low Birth Weight and SIDS
- Increase in long-term effects on the offspring, such as
  - neurobehavioral defects
  - hypertension
  - type 2 diabetes, obesity
  - respiratory dysfunction
  - impaired fertility

Bruin et al Toxicological Sciences 116: 364-374 2010
Maternal Stress and Preterm Birth

• A prospective cohort study of 1,962 pregnant women in central North Carolina between 1996 and 2000, found **12% delivered preterm**

• Looking at a comprehensive array of psychosocial factors including:
  – life events, social support, depression, pregnancy-related anxiety, perceived discrimination, and neighborhood safety

Maternal Stress and Preterm Birth

- Finding of increased risk of preterm birth among women with high counts of pregnancy-related anxiety, with
  - life events to which the respondent assigned a negative impact weight, and
  - with a perception of racial discrimination

Biobehavioral Pathway from Chronic Stress to Preterm Birth

Length of Gestation

Physiologic Placental CRH Trajectory

Term Birth

Pathologic Placental CRH Trajectory

Preterm Birth

Chronic Stress

Stress Response

Hypothalamic-Pituitary-Adrenal (HPA) Axis

Autonomic Nervous System
Maternal BMI & Child Development at 6 Years of Age

- Children of mothers with BMI >35.0 had greater risk for:
  - Emotional and behavioral symptoms
  - Problems with peer interaction
  - Developmental disorders
  - ADHD
  - Autism Spectrum Disorders
  - Needed more speech therapy, psychological services and other special needs service

- Adjusted for sociodemographic factors

Jo et al Pediatrics. 2015
Epigenetic Changes and Human Diseases

Normal processes
- Development
- Cell differentiation
- Aging

External influences
- Environmental exposures
- Nutrition
- Chemical toxins
- Metals
- Mediators of stress
- Drugs of abuse
- Infection (including HIV)

Adverse health outcomes
- Cancer
- Cardiopulmonary disease
- Autoimmune disease
- Obesity
- Diabetes
- Neurodevelopmental disorders
- Schizophrenia
- Addiction
- Depression

Slide Cutesy of Linda Birnbaum NIEHS 2012
<table>
<thead>
<tr>
<th>Child Outcomes</th>
<th>Risk for Poor Relative to Nonpoor Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead poisoning</td>
<td>$3.5^a$</td>
</tr>
<tr>
<td>Birth to unmarried teenager</td>
<td>$3.1^b$</td>
</tr>
<tr>
<td>Short-stay hospital episode</td>
<td>$2.0^c$</td>
</tr>
<tr>
<td>Grade repetition and high school dropout</td>
<td>$2.0^c$</td>
</tr>
<tr>
<td>Low birthweight</td>
<td>$1.7^d$</td>
</tr>
<tr>
<td>Mortality</td>
<td>$1.7^d$</td>
</tr>
<tr>
<td>Learning disability</td>
<td>$1.4^c$</td>
</tr>
<tr>
<td>Parent report of emotional or behavior problem that lasted 3 months or more</td>
<td>$1.3^e$</td>
</tr>
</tbody>
</table>

**SES Mediators**

| Child abuse and neglect                              | $6.8^f$                                    |
| Depression                                            | $2.3^g$                                    |
| Experiencing violent crimes                           | $2.2^h$                                    |
| Substance abuse                                       | $1.9^i$                                    |
**Cycle of Disadvantage and Disability**

**Potential Outcomes**
- Health concerns
- Neurodevelopmental disabilities
- Child neglect and abuse
- Foster care placement

**Environment**
- Poverty
- Poor community support
- Poor health services
- Poor education

**Risk Factors**
- Infant with increased needs
  - Medical needs
  - Developmental needs
  - Increased irritability
- Mother under stress
  - Increased demands
  - Lack of supports
  - Substance abuse

**Self Worth**
- Despair
- Substance abuse
- Promiscuity

**Pregnancy**
- Limited prenatal care
- Tobacco, alcohol & drug use
- Risk of STD's/HIV

**Newborn Infant**
- Prematurity
- Low birth weight
- Fetal Alcohol Syndrome
Can we make a Difference?

• Absolutely!!!!!!
• Positively!!!!!!
Infant Health

- Maternal-Infant “Bonding”
- Feeding and Nutrition
- Safe Home Environment
- Family Support and Security
- Immunizations
- “Medical Home”
- Early Intervention
- Other Resources
The Medical Home

A medical home is not a building, house, or hospital, but rather an approach to providing comprehensive primary care.

A medical home is defined as primary care that is:

- accessible,
- continuous,
- comprehensive,
- family centered,
- coordinated,
- compassionate, and
- culturally effective.
State Funded Services

- **Babies Can’t Wait**
  - In home evaluations and services
  - Preparation for transition
- **Special Education**
  - Special Needs Preschool
  - Individual Education Plans
- **Children with Special Health Care Needs**
  - Cerebral Palsy, sensory impairment, etc
  - Additional funding for services
Home-Based Early Intervention

- Impact of EI on children of high resource (HR) & low resource (LR) families
- LR children displayed greater improvement with EI than HR children
- LR children receiving EI did not differ significantly from HR children

Early Intervention and Cognitive Development PEDIATRICS 137:4, April 2016
Summary

• Vulnerability of premature infants to Health, Developmental & Behavioral problems
• Increased prevalence, increased likelihood of consequences and decreased likelihood of identification and services for children of families of low socioeconomic circumstances
• Our responsibility is to identify at-risk children as early as possible and to provide appropriate early support and intervention
Thank you…
The Perry Preschool Program

• Poor children with low IQ
• Beginning at age 3 and lasting 2 years:
  – 2.5-hour preschool program weekdays during the school year,
  – supplemented by weekly home visits by teachers
• Follow-up at ages 15, 19, 27, and 40

The Perry Preschool Program

A. Data from the Perry Program collected when the individuals were 27 years old (High/Scope). >10th percentile achievement indicates children who scored above the lowest 10% on the California Achievement Test (1970) at age 14; HS Grad indicates number of children who graduated High School on time.

Value-Added Teachers and Student Outcomes

• Researchers in Economics at Harvard and Columbia universities
• Tracked one million children from a large urban school district from 4th grade to adulthood looking at the outcomes of having a Value-Added Teacher

Long-Term Impact on Student Outcomes

• Students assigned to higher VA teachers are more successful in many dimensions:
  – more likely to attend college,
  – earn higher salaries,
  – live in better neighborhoods, and
  – save more for retirement.

Rates of return to human capital investment

- Preschool programs
- Schooling
- Job training

Rate of return to investment in human capital vs. Age

Preschool  School  Post-school

Opportunity cost of funds

Skill Formation and the Economics of Investing in Disadvantaged Children
James J. Heckman in: Science June 30, 2006 VOL 312 page 1900
Resilience Promoting Factors

- Loving and supportive environment
- Positive relationships with adults and peers
- Supportive, attentive and responsible parenting
- Good education
- Healthy diet
- Healthy exposure to outdoor activities and communion with nature

Adapted from Wu et al Frontiers in Behavioral Neuroscience 2013
Conclusions

• The fetus is exquisitely sensitive to environmental influences

• These influences may cause immediate or long term consequences on the health, growth and development of the child and even on the child’s reproductive health

• It is our responsibility to be proactive
  – in raising awareness of the importance of reducing chemical and non-chemical adverse exposures and
  – in actively promoting positive behaviors