Prenatal Alcohol, SIDS, and Stillbirth
PASS Network Mission

In 2003, the National Institutes of Child Health and Development (NICHD) and Alcohol Abuse and Alcoholism (NIAAA) began this Network to develop community-linked studies for investigating the role of prenatal alcohol exposure in the risk for SIDS, stillbirth, and fetal alcohol spectrum disorders (FASD) how these outcomes may be interrelated.


Phase II, 2006-2011: Performance of full-scale, 12,000 subject, hypothesis-driven studies.
The PASS Network:  
Analysis of 12,000 Pregnancies—  
Infant Follow-up to 12 Postnatal Months

**NICHD/NIAAA**  
(NIDCD)  
Project Officers  
Science Officers

**Subcommittees**  
- Genetics  
- Clinical Coordinator  
- Epidemiology  
- Pathology  
- Perinatal Physiology  
- Policies and Protocol

**Advisory and Safety Monitoring Board (ASMB)**

**Steering Committee**

**CCS**  
South Africa  
Tygerberg Hospital

**CCS**  
Northern Plains  
Pine Ridge, SD  
Rapid City, SD  
Sioux Valley, SD  
Spirit Lake, ND

**PAC**  
Columbia University, NY

**DBPC**  
Children's Hospital Boston

**DCAC**  
DM-STAT, Inc., Boston

N=7000  
N=5000
Only the tip of the iceberg

- Fetal Alcohol Syndrome (FAS)
- Partial FAS
- Alcohol-Related Birth Defects (ARBD)
- Alcohol-Related Neurodevelopmental Disorder (ARND)
- Clinical suspect but appear normal
- Normal, but never reach their full potential
- SIDS and Stillbirth?
PASS Specific Aims

- **Epidemiologic analysis of environmental factors**
  - Maternal drinking patterns, amount, and timing
  - Maternal nutrition, psychosocial factors, tobacco intake, others

- **Genetic analysis selected polymorphisms in fetuses, infants, and mothers**
  - Polymorphisms related to alcohol metabolism
  - Polymorphisms related to serotonin, others

- **Autonomic and neurobehavioral factors**
  - Heart rate, heart rate variability, respiration, blood pressure, temperature
  - EEG, hearing Screen, neonatal, 1-month and 1 year neurobehavioral assessment

- **Maternal and placental factors**
  - Doppler analysis
  - Maternal markers (PAPP, α-fetoprotein)
  - Placental histology and immunocytochemistry

- **Brain analysis of selected neurotransmitter systems in fetuses and infants who die**
  - Primary: Serotonin; glutamate; acetylcholine and nicotinic receptors
Secondary Hypotheses

Environmental Modifiers

Fetal Alcohol Exposure

- Placenta Structure and Function
- CNS and ANS Maturation

Genetic Modifiers

Stillbirth
SIDS
FAS/FASD

?
PASS Research Areas

- Epidemiology (including exposure history)
- Maternal Psychological Well-Being
- Infant Dysmorphology
- Maternal Nutrition
- Fetal and Infant Physiology
- Infant Neurodevelopment
- Genetics
- Placental Function and Pathology
- Brain Development and Pathology
Unprecedented Opportunities

- The effects of prenatal alcohol exposure on the risk for perinatal and infant mortality, including stillbirth and SIDS
- The potential links between SIDS and unexplained stillbirth
- Genetic-environmental interactions that influence prenatal toxic exposures
- The effects of prenatal alcohol exposure directly upon:
  - The human placenta
  - Brain development in early human life
  - Physiological development of the autonomic nervous system in early human life
  - Neurobehavioral development in early human life
  - ?
Specimens

- Maternal Saliva (DNA) → 12,000 (collected during prenatal visits)
- Maternal Blood (AFP and PAPP-A)$^{STEEL}$ → $7062 \times 2 = 14,124$ samples
- Guthrie Card (DNA) → >12,000 (collected at delivery, in the event of a stillbirth, or in the event of an infant death)
- Maternal Blood → 12,000 (collected at delivery)
- Umbilical Cord Blood → 12,000 (collected at delivery)
- Meconium (FAEE)$^{CDC}$ → 6,000 (collected at delivery)
- Placenta → 3,841 (collected at delivery): 2,867 from Cape Town and 974 from the Northern Plains
- Brain Tissue → 74 (collected in the event of an infant death) 98 (collected in the event of a stillbirth)
Ultrasound Measures

**Biometry**
- Biparietal diameter
- Head circumference
- Abdominal circumference
- Femur length
- Humerus length

**Doppler flow velocity**
- Umbilical artery
- Uterine artery
- Middle cerebral artery
- Ductus venosus arteriosus
Serotonin Hypothesis in SIDS

- Genetic Factors → UNKNOWN CAUSE(S) → Environmental Factors

- ABNORMAL CAUDAL 5-HT Domain

- ↓ CO₂ sensitivity
- Arousal Deficit
- Respiratory Pattern Abnormality
- Altered blood pressure recovery
- Altered temperature control
- Altered airway reflexes

- Critical Period

- Convergence of Faulty Reflexes

- Exogenous Stressor

- SIDS
The Rostral and Caudal Domains of the Serotonergic (5-HT) Brainstem System

Rostral Domain (upper brainstem): Cognition and Affective Behavior

Caudal Domain (lower brainstem): Integration and modulation of respiration, autonomic control, central chemosensitivity, temperature regulation, upper airway reflexes
Physiology Assessment Protocols

• Assessment of Fetal Physiology
  – Gestational Ages in Weeks: F1 (20-24), F2 (28-32), F3 (36+)
  – Dependent Variables
    • Heart Rate, Heart Rate Variability
    • Fetal Movement
    • Fetal Heart Rate Movement Coupling
    • Doppler Flow Velocity Waveforms (Uterine and Middle Cerebral Arteries)

• Infant Sleep Physiology and Cardiorespiratory Tilt Challenge
  – Neonate (1-3 days) and Infant (1-month)
  – Dependent Variables
    • Basal Heart Rate and Variability, Respiration, Temperature, Blood Pressure, Movement, and Sleep State
    • Cardiorespiratory Response to 45° Tilt
    • Heart Rate/ Movement Coupling
PASS Clinical Sites

- North & South Dakota
- South Africa
Physiologic Assessments of the Fetus

Fetal Heart Rate

Fetal Movement

1 Minute
Fetal ECG

Monica Healthcare
PASS Network Long-Term Goal

To decrease fetal and infant mortality and to improve child health.