# Highlights of NICHD Stillbirth Research

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# Stillbirth research

- Basic science, translational and clinical research
  - SCRN
    - » Scope, causes, pathophysiology
  - nuMoM2b
    - » Prediction, pathophysiology
  - MFMU clinical trials- CMV, ARRIVE
    - » prevention
  - PASS
    - » Causes, pathophysiology

# Stillbirth Collaborative Research Network (SCRN)

- **Population-based case-control study**
  - 5 geographic catchment areas defined *a priori* by county lines
  - 59 hospitals averaging > 80,000 deliveries per year
  - SBs and LBs enrolled at delivery (3/2006-8/2008)
  - All SBs (residents of catchment areas)
  - Representative sample of LBs
  - Goal:
    - Examine risk factors for and causes of SB

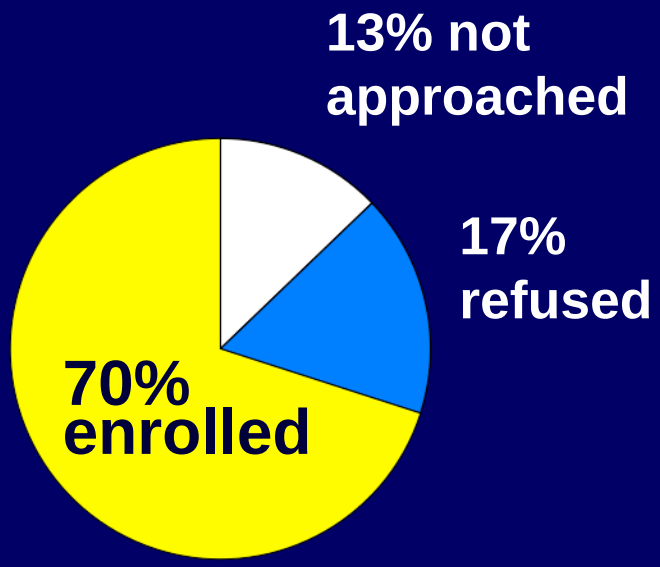
Stillbirth Collaborative Research Network

# Case-control Protocol

- In-hospital maternal interview
- Medical record abstraction
- Standardized postmortem (SBs) and placental pathology (SBs and LBs)
- Clinically indicated tests (SBs)
- Biospecimen collection
  - fetal samples (SBs)
  - maternal and cord blood, placental samples (SBs and LBs)

# Enrollment of Eligible Women

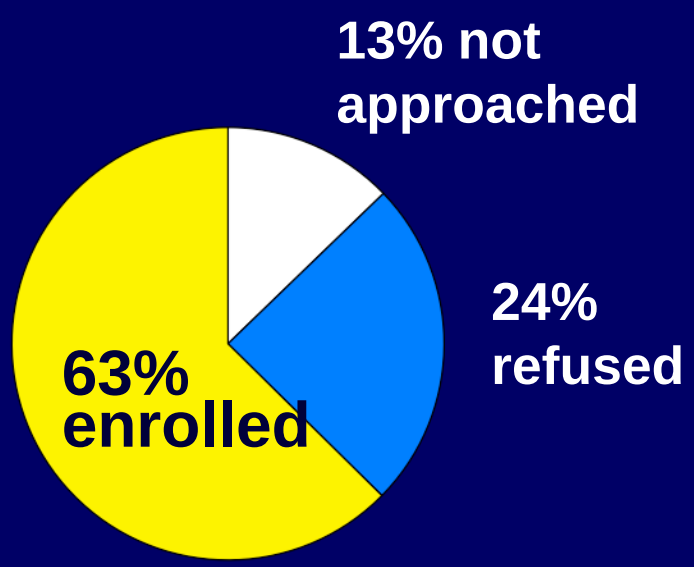
## Stillbirths




958 Eligible SBs

663 Enrolled SBs

## Livebirths

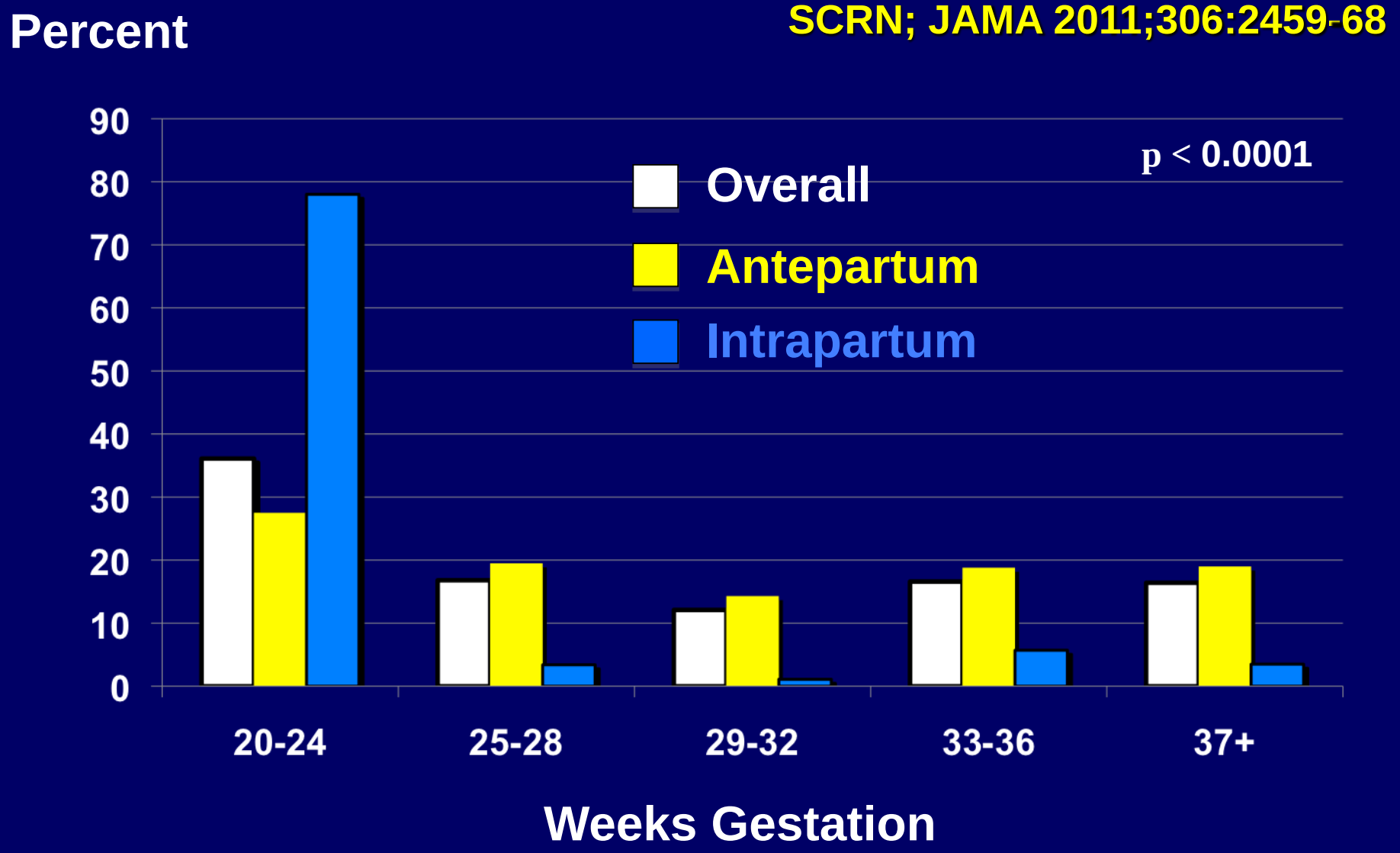



3,084 Eligible LBs

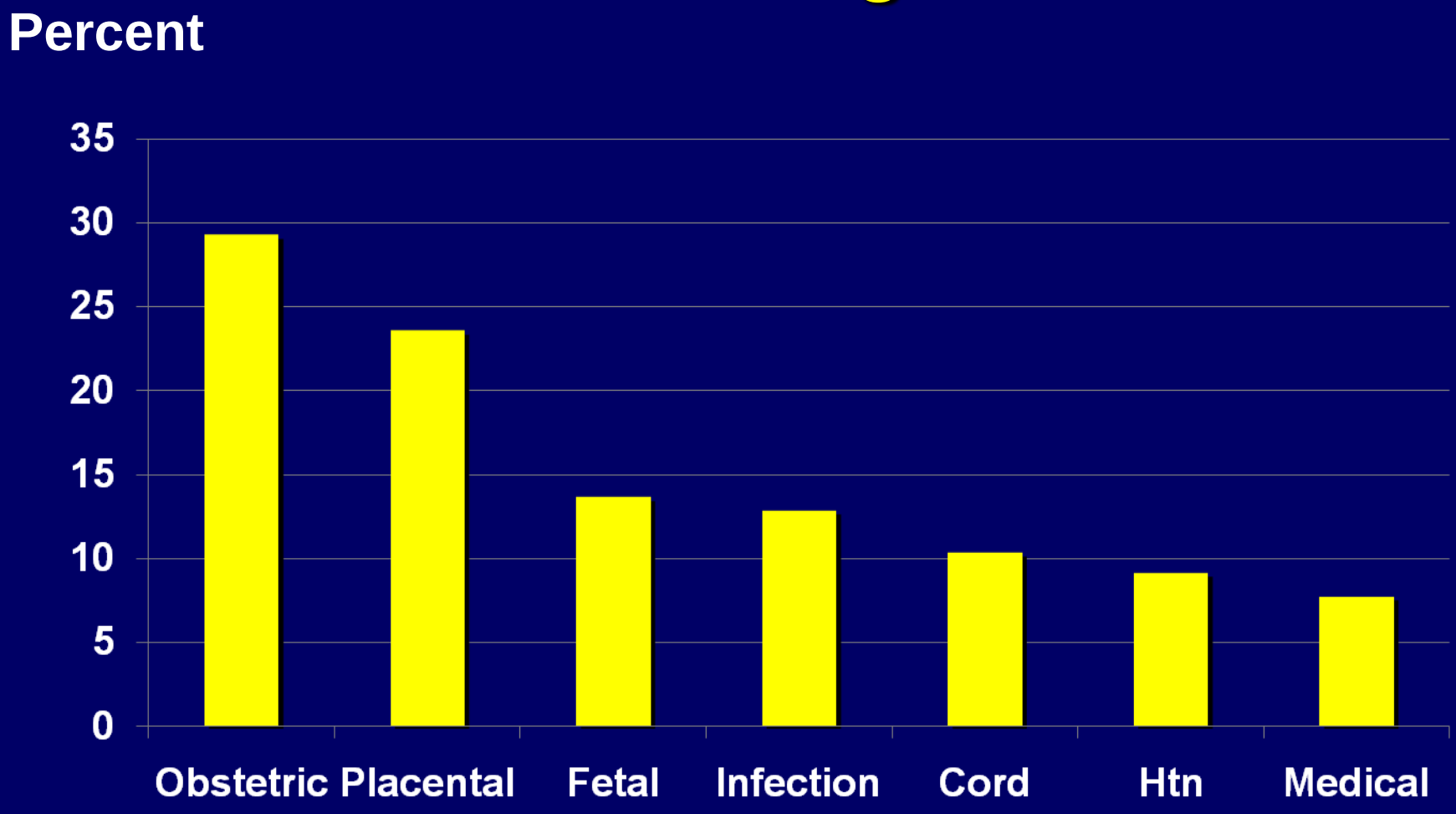
1,932 Enrolled LBs

# Timing in Gestation of Stillbirths

SCRN; JAMA 2011;306:2459-68

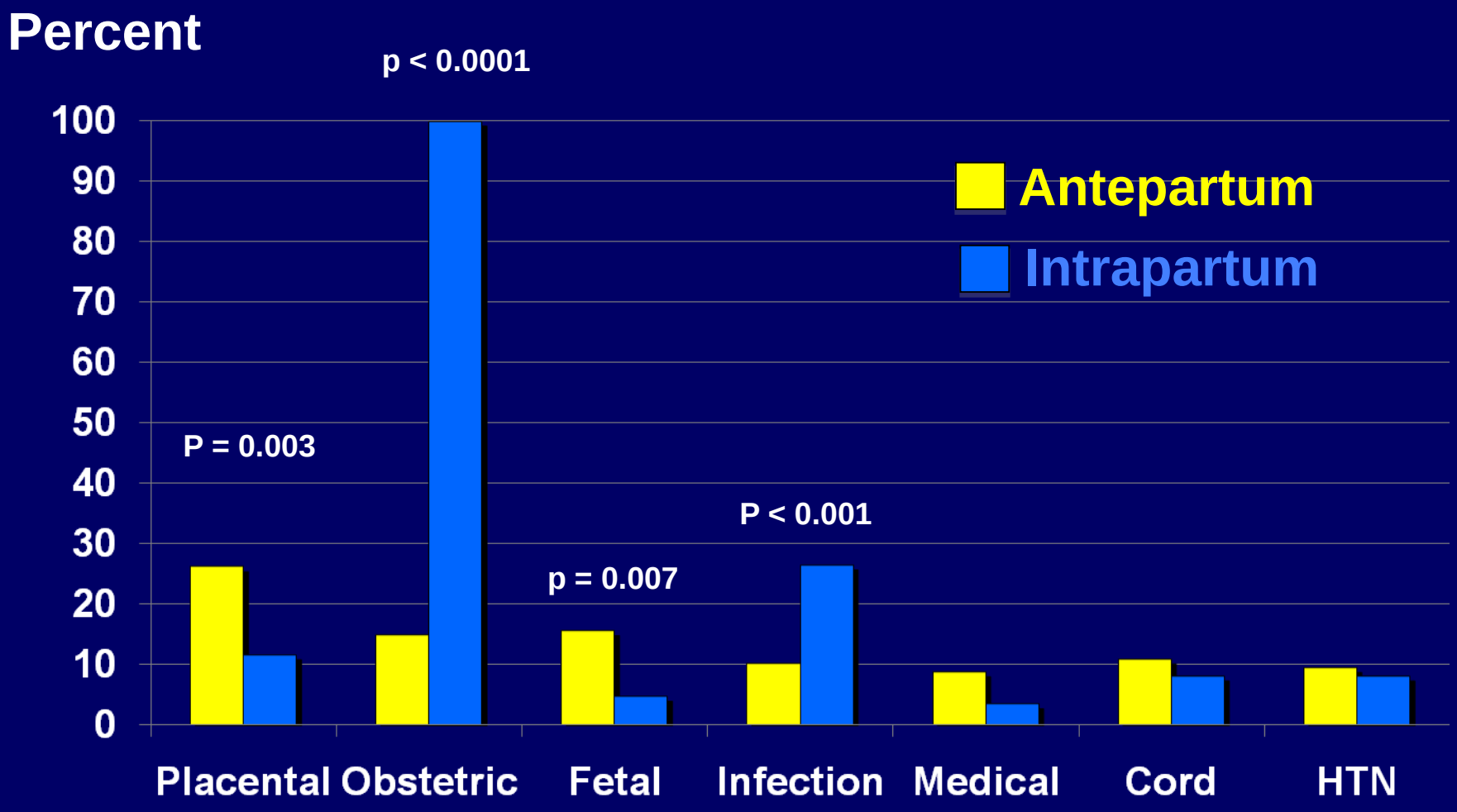


# Probable / Possible Cause of Death Broad Categories




SCRN; JAMA 2011;306:2459-68

# Probable / Possible Cause of Death by Timing of Death




SCRN; JAMA 2011;306:2459-68

# SCRN Publications


- Parker CB, et al. Stillbirth Collaborative Research Network: design, methods and recruitment experience. *Paediatr Perinat Epidemiol*. 2011; 25(5):425-35.

- Pinar H, et al. The Stillbirth Collaborative Research Network (SCRN) Placental and umbilical cord examination protocol. *Am J Perinatol* 2011 Dec;28(10):781-92.

- Pinar H, et al. The Stillbirth Collaborative Research Network Postmortem examination protocol. *Am J Perinatol* 2012;29(3):187-202.

- Pinar H, et al. The Stillbirth Collaborative Research Network Neuropathologic examination protocol. Am J Perinatol. 2011;28(10):793-802.

- Dudley DJ, et al. A New System for Determining the Causes of Stillbirth. *Obstet Gynecol* 2010, 116:254-60.

# SCRN publications

- Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. *JAMA* 2011;306:2469-79.
- Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. *JAMA* 2011;306:2459-68
- Reddy UM et al. Karyotype versus microarray testing for genetic abnormalities after stillbirth. N Engl J Med 2012;367:2185-93.
- Conway DL et al. An alogorithm for the estimation of gestational age at time of fetal death Paediatr Perinat Epidemiol 2013;27:145-57
- Silver RM et al. Antiphospholipid Antibodies in Stillbirth. Obstet Gynecol 2013;122:641-657.

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# SCRN publications

- Hogue CJ et al. A Population-based Case-Control Study of Stillbirth: The Relationship of Significant Life Events to the Racial Disparity for African Americans. Am J Epidemiol 2013; 177:755-67

- Silver RM, et al. Bile acids in a multi-center, population-based case control study of stillbirth. *Am J Obstet Gynecol* 2013 Nov 8. pii: S0002-9378(13)02016-4. doi: 10.1016/j.ajog.2013.11.017.

- Varner MW et al. Association between Stillbirth and Illicit Drug Use and Smoking During Pregnancy. Obstet Gynecol 2014;123:113-125

- Pinar H et al. Placental Findings in Singleton Stillbirths. Obstet Gynecol 2014;123:325-336

- Bukowski RK et al. Fetal Growth and Risk of Stillbirth: A Population- Based Case-Control Study. Plos Med. In press

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# Future SCRN studies

- Maternal and placental infections in stillbirth
- Microbiome of stillbirths of suspected infectious etiology
- Placental abnormalities in women with preeclampsia and thrombophilia that increase the risk for stillbirth
- Placental pathology in stillbirths with growth abnormalities (SGA or LGA). Are these associated with specific maternal medical conditions or other characteristics?
- Placental pathologies and/or fetal growth abnormalities associated with abnormalities on microarray among stillbirths
- Race-specific patterns of risk for stillbirth
- Increased risk of stillbirth among obese women

SCRN
Stillbirth Collaborative Research Network

# NICHD Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be (nuMoM2b) RFA-HD-08-029

## Sleep Disordered Breathing During Pregnancy and Risks to Cardiovascular Health

## (Sleep Breathing Sub-study)

## NHLBI

nuMOM2b
Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be

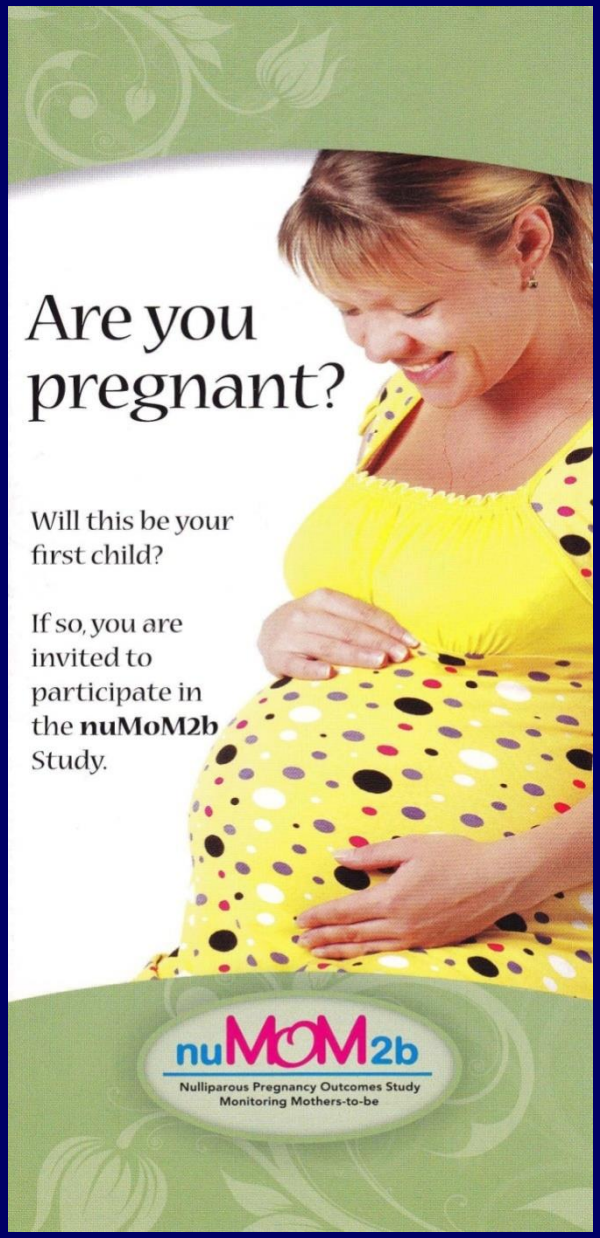
# Adverse Pregnancy Outcomes

- Pregnancies often complicated
  - Preterm birth
  - Preeclampsia / gestational high BP
  - Fetal growth restriction
  - Stillbirth
- Interventions in subsequent pregnancies to reduce the risk of recurrent pregnancy complications

# Adverse Pregnancy Outcomes

- **Complications more common in first pregnancy**
- **40% of pregnancies (USA) are first pregnancies**
- **Limited clinical strategies to predict or prevent complications in first pregnancy**
- **Etiology and pathophysiology of APO**
- **Predictive measures and treatment modalities**

# nuMoM2b




Large prospective observational cohort

10,000 singleton pregnancies

Multi-center (8 sites)

- Case Western Reserve University
- Columbia University
- Indiana University
- University of Pittsburgh
- Northwestern University
- University of California – Irvine
- University of Pennsylvania
- University of Utah
- RTI International – DCC

# NuMoM2b Overarching Goals

- Determine characteristics including biomarkers and environmental factors that predict adverse outcomes
- Identify aspects of placental development that influence adverse outcomes
- Characterize fetal genetic and growth parameters that are associated with adverse outcomes

# NuMoM2b Protocol

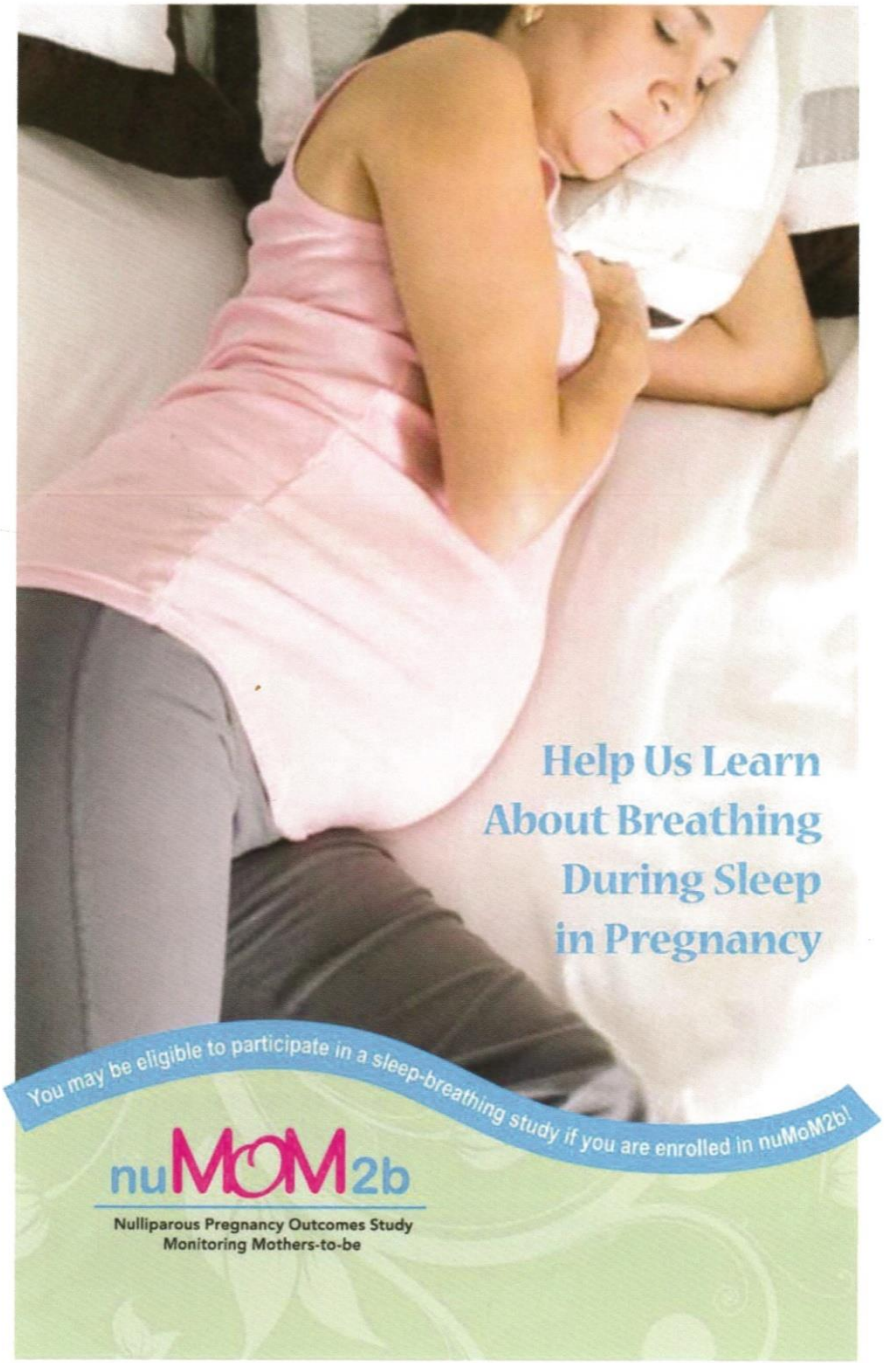
V1
6 – 13 6/7 wks

V2
16 – 21 6/7 wks

V3
22 – 29 6/7 wks

Comprehensive clinical and biospecimen data

- **Ultrasound**
- **Clinical measures**
- **Biospecimens (blood, urine, cervico-vaginal secretions)**
- **Delivery specimens (placenta)**
- **Maternal and fetal outcomes**


Help Us Learn
About Breathing
During Sleep
in Pregnancy
You may be eligible to participate in a sleep-breathing study if you are enrolled in nuMoM2b!
nuMOM2b
Nulliparous Pregnancy Outcomes Study
Monitoring Mothers-to-be

# Sleep Sub-study

- Primary Aim: Sleep disordered breathing (SDB) is a risk factor for APO among nulliparas

- SDB leads to pathophysiology similar to APO
  - Increased sympathetic tone
  - Oxidative stress
  - Systemic inflammation
  - Insulin resistance
  - Hyperlipidemia

- SDB may be a modifiable risk factor for adverse pregnancy outcomes

# Sleep Sub-study Protocol

- Large prospective observational cohort
- 10,000 singleton pregnancies
  - Questionnaires / Clinical data
- 3,630 singleton pregnancies
  - Subset of the nuMoM2b parent cohort
  - Objective measures of sleep disordered breathing (SDB) with Embletta Gold device

# Stillbirth
# Cytomegalovirus (CMV)

- Most common congenital viral infection
- 1% of pregnant women acquire primary CMV during pregnancy
- Primary CMV
  - Highest rate of transmission
  - Most severe consequences
- Stillbirth
- Placental damage
- Fetal growth restriction
- Direct fetal effects including hydrops

# A Randomized Trial to Prevent Congenital CMV

- Does maternal administration of hyperimmune CMV globulin lower congenital CMV infection among offspring of women diagnosed with primary CMV infection before 23 weeks?
- Intervention: IV CMV hyperimmune globulin (100mg/kg) or IV placebo
- Primary outcome: Stillbirth or neonatal congenital CMV infection
- Sample size: 800 women
- Status: 110 enrolled

# A Randomized Trial of Induction Versus Expectant Management (ARRIVE)

- Does elective induction of labor in nulliparous women at 39 weeks improve perinatal outcome compared with expectant management?

- Primary Outcome-composite of stillbirth or neonatal death or severe neonatal morbidity

- Sample size= 6000

# Prenatal Alcohol in SIDS and Stillbirth (PASS) Network

- Network of 5 cooperative agreements with NICHD, NIAAA and NIDCD
  - Clinical Sites:
    - » Northern Plains- Sanford Health;
    - » Cape Town SA, Stellenbosch University
  - Developmental Biology & Pathology Center: Boston Children's Hospital
  - Physiology  Assessment Center, Columbia University
  - Data Coordinating Center, DM-STAT

- Phase II: Cohort study from pregnancy through infancy to assess the role of prenatal alcohol exposure in SIDS and stillbirth risk.
  - Longitudinal assessments from 6 weeks gestation through one year of life
- Over 10,000 pregnant women enrolled of 12,000 target
- Enrollment and follow-up anticipated to be completed in 2016

# Hypotheses

- **Primary hypothesis:** Prenatal alcohol exposure increases the risk for SIDS and stillbirth.

- **Secondary hypothesis**: The interaction among environmental and genetic factors affects the risk for a spectrum of disorders related to prenatal alcohol exposure from mid-gestation through infancy, including SIDS, stillbirth, and the early manifestations of Fetal Alcohol Syndrome and Fetal Alcohol Spectrum Disorder.

# PASS Pregnancy and Infant Outcomes

PRIMARY

- SIDS *: Unexplained sudden death occurring before 1 year of age
- Stillbirth*: Fetal demise ≥20 weeks gestation

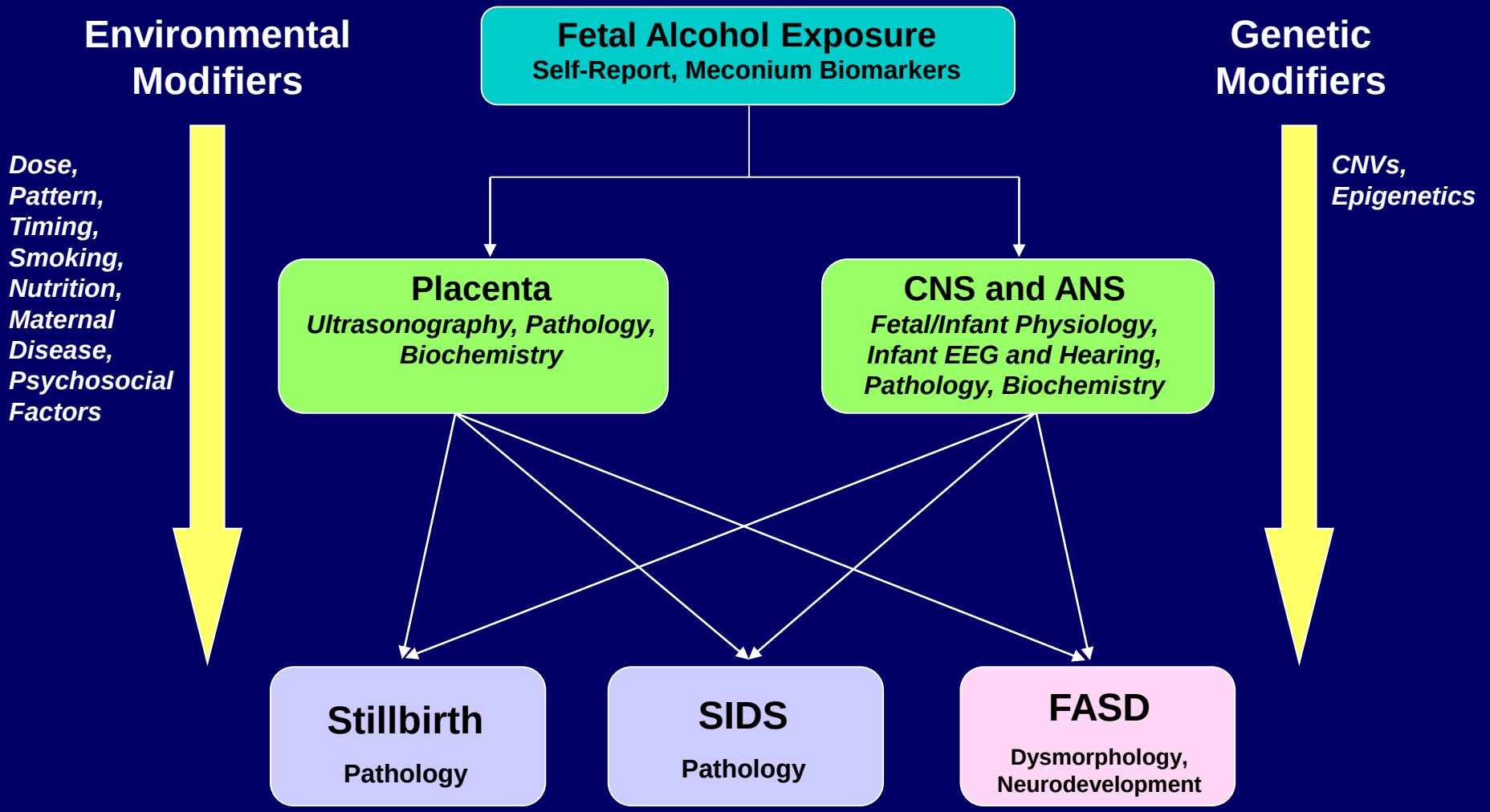
SECONDARY

- FASD*: Spectrum disorder encompassing adverse neurobehavioral and physical outcomes from prenatal alcohol exposure
- In-hospital infant deaths
- Miscarriage: Fetal demise <20 weeks gestation
- Prematurity: Birth <37 weeks gestation

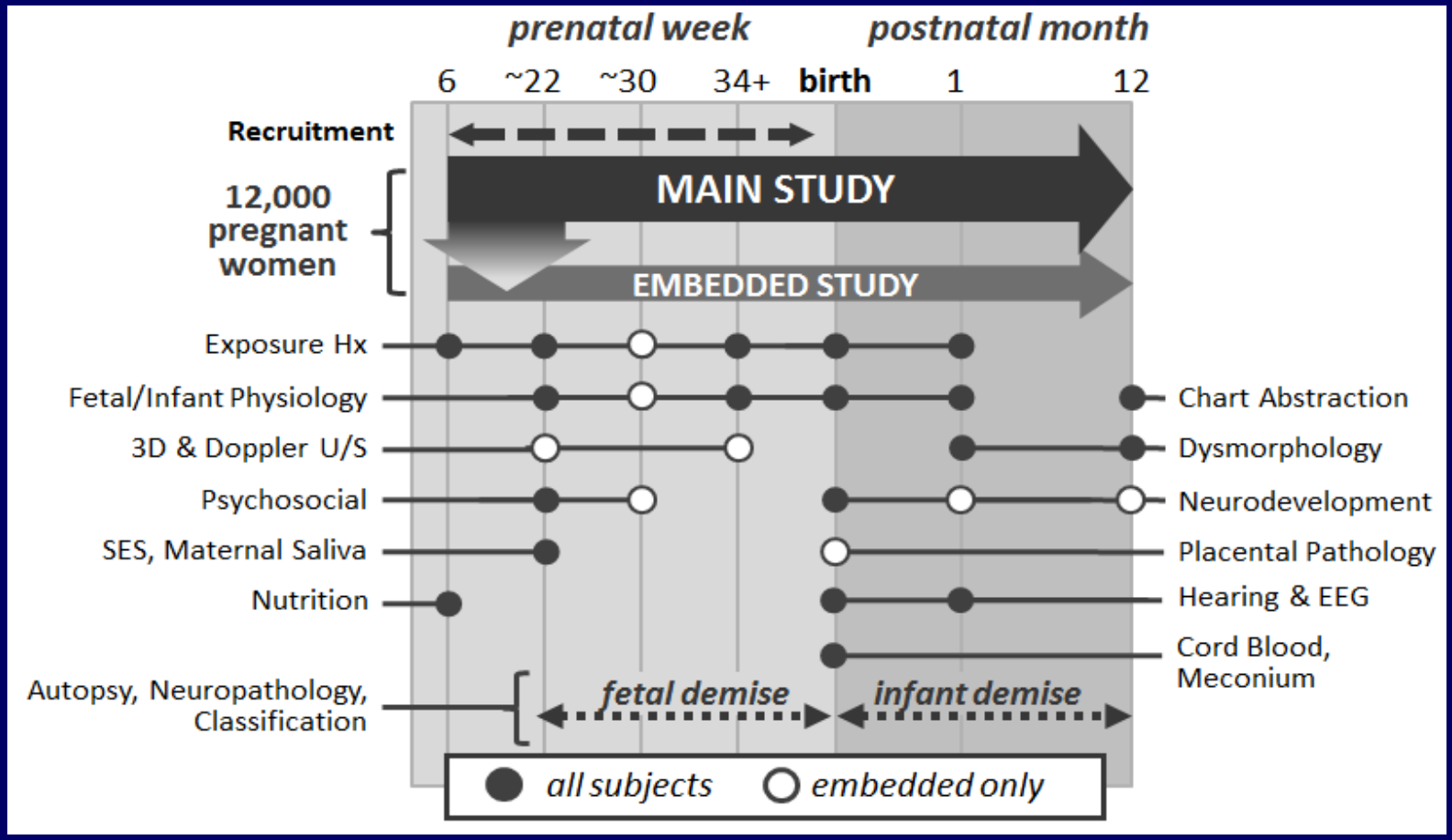
**All outcomes adjudicated by case review*

PA; Updated August 2011

# Multidisciplinary Approach



# Common Study Protocol




Schedule of Evaluations and Events
3D = three-dimensional
Hx = history
U/S = ultrasound

# PASS Opportunities

- Prospective study of the regulation of fetal and infant brain development
- Potential public health impact through early identification (in the fetal and infant period) of children at risk for adverse outcomes related to prenatal alcohol exposure
- Elaboration of genetic susceptibility and molecular mechanisms of SIDS, stillbirth, and fetal alcohol related neurological disorders
- Potential to shed light on the etiology and pathogenesis of SIDS and stillbirth, and how they may be related.