Stillbirth Assessment, Management and Prevention

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Disclosures

• I have no relevant financial relationships to disclose or conflicts of interest to resolve.

• I will not discuss any unapproved or off label, experimental or investigational use of a product, drug, or device.
Objectives

• Define stillbirth and impact in obstetrics
• Describe etiologies and conditions associated with stillbirth
• Describe the “workup” for stillbirth
• Describe management of subsequent pregnancy
• Research
Infant mortality rate has decreased more than stillbirth rate in U.S.

Infant mortality rate has decreased more than stillbirth rate in U.S.

- U.S. Stillbirth rate = 5.96 per 1,000 births (2013)
  - 23,595 stillbirths
  - 1/165 pregnancies
- Lack of decline in stillbirth past decade + decline in infant mortality
  - Stillbirth rate exceeded infant mortality rate for the first time!
- Arizona stillbirth rate = 5.86 per 1,000 births
Rates of early and late stillbirths are equal

Stillbirth rates worldwide

2.65 million third trimester stillbirths each year
Applying high-income country stillbirth definitions (including second trimester) this number may be 40% higher.

Stillbirth rates (deaths per 1000 livebirths)

Lowest 2 countries
1. Finland (2)
2. Singapore (2)

Highest 2 countries
192. Nigeria (42)
193. Pakistan (47)

10 countries account for 66% of the world’s stillbirths – and also 66% of neonatal deaths and over 60% of maternal deaths

1. India
2. Pakistan
3. Nigeria
4. China
5. Bangladesh
6. Dem Rep Congo
7. Ethiopia
8. Indonesia
9. Tanzania
10. Afghanistan

Stillbirth: Risk factors and etiologies

- Maternal Conditions
- Fetal Conditions
- Obstetric Conditions
- Other Conditions
- Unexplained
# Stillbirth: Maternal Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>SB Rate / 1,000</th>
<th>SB: Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic HTN</td>
<td>6.0 - 10.0%</td>
<td>6 - 25</td>
<td>1.5 - 4.0</td>
</tr>
<tr>
<td>Mild PE</td>
<td>5.8 - 7.7%</td>
<td>9 - 51</td>
<td>1.2 - 4.0</td>
</tr>
<tr>
<td>Severe PE</td>
<td>1.3 - 3.3%</td>
<td>12 - 29</td>
<td>1.8 - 4.4</td>
</tr>
<tr>
<td>Diabetes (diet)</td>
<td>2.5 - 5.0%</td>
<td>6 - 10</td>
<td>1.2 - 2.4</td>
</tr>
<tr>
<td>Diabetes (insulin)</td>
<td>2.4%</td>
<td>6 - 35</td>
<td>1.7 - 7.0</td>
</tr>
<tr>
<td>SLE</td>
<td>&lt;1%</td>
<td>40 - 150</td>
<td>6 - 20</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>&lt;1%</td>
<td>15 - 200</td>
<td>2.2 - 30</td>
</tr>
<tr>
<td>Thyroid Disorders</td>
<td>0.2 - 2%</td>
<td>12 - 20</td>
<td>2.2 - 3.0</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>1 - 5%</td>
<td>18 - 40</td>
<td>1.2 - 5.0</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>&lt;0.1%</td>
<td>12 - 30</td>
<td>1.8 - 4.4</td>
</tr>
</tbody>
</table>

SCRN, JAMA 2011;306:2469 - 79
U.S. Stillbirth Rates in 2013 by Maternal Race / Ethnicity

Rate per 1,000 live births and fetal deaths in specified group

- Total: 5.96
- Non-Hispanic white: 4.88
- Non-Hispanic black: 10.53
- American Indian or Alaska Native: 6.22
- Asian or Pacific Islander: 4.68
- Hispanic: 5.22

Maternal age

Reddy; Am J Obstet Gynecol 2006;195:764-70
Assisted Reproductive Technologies

- Increased multiple gestation
- 4-fold increased SB risk for singleton IVF/ICSI pregnancies vs. spontaneous
- Reason for increased SB risk is unclear
- Risk: IVF/ICSI increased SB risk compared to women with time to pregnancy ≥ 1 year or use of non-IVF ART

Wisborg; Hum Reprod 2010;25:1312
Obesity and Risk of Stillbirth

• Maternal obesity is associated with conditions that increase stillbirth risk
  • Diabetes
  • Major Congenital Abnormalities
  • Preeclampsia
  • Obstructive sleep apnea
• Independent stillbirth risk factor

Cedergren MI. Obstet Gynecol, 2004
Smoking

• 36% increase in the odds of stillbirth (Flenady, Lancet, 2011)

• Women quit smoking from first to second pregnancy reduce stillbirth risk to that of nonsmokers in second pregnancy (Hogberg, BJOG, 2007)
Stillbirth – Fetal Conditions

- Genetic
- Infection
Stillbirth – Genetic Conditions

- Chromosomal abnormalities
- Syndromes / malformations
- Single gene disorders
- X-linked conditions
- Autosomal dominant mutations
- Confined placental mosaicism
Genetic Conditions
Chromosomal Abnormalities

• 6-12% of stillbirths (10 times the rate in live born)
• Rate underestimated- failure to culture cells
• Increased with malformations / early loss
• Monosomy X (23%), trisomy 21 (23%), trisomy 18 (21%), and trisomy 13 (8%).
• Karyotype particularly indicated if:
  • History of recurrent losses
  • Family history of abnormal offspring
  • FGR
  • Malformations or hydrops present
Stillbirth – Infections

• 10 - 25% of fetal deaths
• Higher in developing countries
• More common at early gestational ages (developed countries)
Mechanism of Stillbirth Infection

- Direct fetal infection
  - Damage organs
  - Developmental abnormalities

- Placental damage

- Severe maternal illness

- Intra-uterine infection
  - Preterm labor
Parvovirus B19

- 8% of stillbirths by PCR in Sweden
- Virus trophic for fetal red blood cell precursors and cardiac cells
  - Anemia
  - Hydrops
- Direct myocardial damage
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
• Placental damage
• FGR
• Direct fetal effects
Stillbirth – Syphilis

- Treponema pallidum (spirochete)
- 25 - 50% of stillbirths in some African populations
- Direct fetal and placental infection
- 50% rate of stillbirth (untreated)
- 30% rate of congenital syphilis
- Over 1 million cases of congenital syphilis per year
- Preventable cause of stillbirth through screening and treatment in pregnancy!
Stillbirth – Transplacental Bacterial Infection

• Listeria monocytogenes
  • Unpasteurized soft cheese
  • Undercooked meat
  • Villous necrosis and microabscesses in the placenta
  • Direct fetal infection

• Many other rare causes such as TB, tularemia, clostridia, anthrax, typhoid fever, brucellosis, haemophilus influenza
Stillbirth – Ascending Bacterial Infection

• Very common
• The same organisms that cause chorioamnionitis
  • Mycoplasma / ureaplasma
  • Group B streptococcus
  • E. coli
  • Klebsiella
  • Enterococcus
  • Bacteroides
Zika Virus: First Cohort Study

42 Zika+ pregnant women with acute symptoms of Zika infection in Brazil followed with serial ultrasound

29% with fetal anomalies

17% with microcephaly, atrophy, or calcifications

2 Stillbirths at 36 and 38 weeks
Stillbirth – Obstetric Conditions

- Abruption
- Preeclampsia
- Cord prolapse
- Cervical insufficiency
- Preterm labor
- Preterm premature rupture of membranes
Obstetric Conditions – Fetal-Maternal Hemorrhage

• 1 - 14% of all stillbirths
• Volume of blood transfused
• ~ 50 -75% of total fetoplacental blood volume
• Reliable method for identification and quantification of FMH (prior to labor induction)
• Evidence of hypoxia and anemia on autopsy
Obstetric Conditions – Umbilical cord accidents

• Many cases attributed to cord accident
• Possible mechanisms:
  • Cessation of blood flow
  • Intermittent disruption of blood flow
  • Fetal blood loss
  • Cord entanglement – 30% of normal pregnancies
• Causality: Cord occlusion and hypoxic tissue injury on autopsy, and exclude other accepted causes of stillbirth.
• True knots also common in live birth
Stillbirth Collaborative Research Network (SCRN)

- Population-based study
- 2006 - 2008
- 5 geographic catchment areas defined *a priori* by county lines
- 59 hospitals averaging >80,000 deliveries/year
- 663 stillbirths and 1932 live births
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)
Stillbirths (Cases): Results

- 663 stillbirths enrolled
- 512 – complete postmortem exams
  - 425 (83%) antepartum stillbirth
  - 87 (17%) intrapartum stillbirth
- Race
  - White / Non-Hispanic: 35.7%
  - Black / Non-Hispanic: 22.5%
  - Hispanic: 34.4%
  - Other: 7.2%
INCODE
Initial Causes of Fetal Death

• **Probable**: high likelihood

• **Possible**: reasonable certainty - involved in a pathophysiologic sequence

• **Present**: conditions of interest

• May have ≥ 1 cause

INCODE
Causes of Death: Broad Categories

- Placental conditions
- Obstetric complications
- Fetal / genetic abnormalities
- Infections
- Maternal medical conditions
- Umbilical cord abnormalities
- Hypertensive disorders
Stillbirths: Cause of Death?

• 60.9% - probable cause
• 76.2% - possible or probable cause
• 31.4% - more than one possible or probable cause

SCRN; JAMA 2011;306:2459-68
Probable / Possible Cause of Death
Broad Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric</td>
<td>35%</td>
</tr>
<tr>
<td>Placental</td>
<td>30%</td>
</tr>
<tr>
<td>Fetal</td>
<td>25%</td>
</tr>
<tr>
<td>Infection</td>
<td>20%</td>
</tr>
<tr>
<td>Cord</td>
<td>15%</td>
</tr>
<tr>
<td>Htn</td>
<td>10%</td>
</tr>
<tr>
<td>Medical</td>
<td>5%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
</tr>
</tbody>
</table>
Probable / Possible Cause of Death by Race / Ethnicity

- Obstetric
- Infection
- HTN
- Medical

P < 0.001

White
Black
Hispanic

SCRN; JAMA 2011;306:2459-68
Probable / Possible Cause of Death by Race / Ethnicity

- Placental
- Fetal
- Cord
- None

Percent

White
Black
Hispanic

SCRN; JAMA 2011;306:2459-68
SCRN – Utility of test in determining cause of death

- Placental histology: 64.6%
- Autopsy: 42.4%
- Karyotype/Microarray: 11.9%
- Antiphospholipid antibodies: 11.1%
- Fetal maternal hemorrhage: 6.4%
SCRN – Utility of test in determining cause of death

- Glucose screen: 1.6%
- Parvovirus serology: 0.4%
- Serologic test for syphilis: 0.2%
- Utility of the tests varied by clinical presentation, suggesting a customized approach for each patient.

Page, Obstet and Gynecol, 2017
Genetic Conditions

Microarray

- Genetic testing for pregnancy loss
- Does not require live cells!
- Identification of abnormalities not ascertained by karyotype- smaller deletions and duplications (copy number changes)
- SCRN – 532 stillbirth array and karyotype
- Success: 85.5% array vs 70.5% karyotype
- More abnormalities identified with array:
  - All stillbirths: ↑41.9%
  - Antepartum stillbirths: ↑34.5%
  - Anomalous stillbirths: ↑53.8%

Stillbirth: Infection Evaluation

- Clinical history
  - Maternal illness / obstetric complications
- Placental histology
- Fetal autopsy
- Routine cultures NOT useful
  - Vaginal delivery – contamination
- Routine serology NOT useful
- Routine TORCH titers NOT useful
- Targeted studies based on clinical history, placenta and autopsy
Evaluation of Stillbirth: Why?

- Facilitates grieving and “closure”
- Recurrence risks
- Sporadic cause- reassurance
- May improve subsequent outcome
- Fewer unexplained cases with systematic evaluation
Optimal Evaluation of Stillbirth

• CONTROVERSIAL
• Cost versus yield
• Focus on common causes
• Focus on recurrent conditions
• Pay attention to clues
• Emotionally challenging:
  • Varied levels of comfort with autopsy or genetic testing
Generally accepted tests

- Clinical history
- Fetal autopsy
- Placental evaluation
- Karyotype/Microarray
- Screen for fetal-maternal hemorrhage
- Lupus anticoagulant screen
- Anticardiolipin antibodies

ACOG Practice Bulletin, 2009; Page, Obstet Gynecol, 2017
SCRN; JAMA 2011;306:2459-68
Korteweg; Am J Obstet Gynecol 2012
Useful in some cases (If “clues” present)

- Testing for specific organisms
- Screening for diabetes
- Toxicology screen
- Assessment of thyroid function
- Antibody screen
- Syphilis serology

ACOG Practice Bulletin, 2009; Page, Obstet Gynecol, 2017
SCRN; JAMA 2011;306:2459-68
Korteweg; Am J Obstet Gynecol 2012
Not Useful

- Placental cultures
- Routine TORCH titers
- ANA testing
- Testing for large numbers of thrombophilias
- Bile acids / glycohemoglobin / thyroid function if no features of disease

ACOG Practice Bulletin, 2009
SCRN; JAMA 2011;306:2459-68
Korteweg; Am J Obstet Gynecol 2012
Hospital Care for Parents After Perinatal Death

- 1,100 articles from 1966 - 2006 on fetal death in second or third trimester, neonatal death in first month
- 60 eligible studies were included
- 6200 parents

Gold KJ, Obstet Gyencol 2007
Recommendations for Improving Hospital Care After Perinatal Death

• Allow parents to help decide when to deliver
• Provide parents the option for post-delivery care on or off a maternity floor
• Be sensitive to physical pain during delivery and offer adequate pain control. Avoid oversedation
• Encourage parents to see and hold their infants for extended periods and at multiple sittings and offer who initially decline additional chances later
Recommendations for Improving Hospital Care After Perinatal Death

• Take nonclinical photographs of cleaned-up infants as soon after delivery. Include a photograph of multiples together even if one or more babies has died

• Collect memorabilia about the baby. If the parents decline initially, offer them again later or hold the materials for a future time

• Discuss options for burial with both parents, allow parents to participate in final decisions
Recommendations for Improving Hospital Care After Perinatal Death

• Ensure autopsy results are provided to parents promptly
• Educate other members of a patient’s obstetric team about interventions valued by bereaved parents
• Offer bereavement services and psychological counseling and close surveillance for development of depression
Subsequent Pregnancy after Stillbirth

• Difficult for couple
  • Anxiety, failure, personal guilt
  • Lack of closure- cause of stillbirth remains unknown (50%), never counseled postpartum

• Difficult for clinicians to optimally counsel, evaluate and manage

• Little is known about pregnancy after experiencing stillbirth
Stillbirth Recurrence Risk (Summary)

• Risks known for a few conditions
• Overall rates:
  • 0-8%
  • Increase: 2 to 10 fold
• Higher risk of loss:
  • Earlier losses
  • Recurrent losses
  • Non-Hispanic Black
  • Fetal growth impairment
• Lower risk of loss:
  • ? Unexplained stillbirth
Prediction: Need to understand the cause of the previous stillbirth

- Congenital anomalies
- Genetic conditions
- Infections
- Placental abnormalities
- Umbilical cord abnormalities
- Fetal - maternal hemorrhage
- Maternal medical conditions
Stillbirth Recurrence Risk

- Most cases are sporadic
- Recurrence risk is low for most families
- In cases at higher risk:
  - Medical interventions
  - Prenatal diagnosis
Stillbirth – Subsequent Pregnancies

- Emotional management
- Reassurance – TLC
- Serial sonograms
- Antenatal surveillance
- Fetal kick counts
- Delivery (at 39 weeks)
- Medical interventions for selected cases
Research
Antenatal Testing- AMA

- > 35 years: 15.3% of all live births (600,000)
- > 40 years: 3.0% of all live births (118,000)
- ACOG: testing not specifically indicated
  “antepartum fetal surveillance has been used in pregnancies in which the risk of antepartum fetal demise is increased.”
- SMFM: “insufficient evidence to confirm that antenatal testing for the sole indication of AMA reduces stillbirth or improves perinatal outcomes”
Antenatal Testing- AMA

- Retrospective cohort, 4469 singleton pregnancies ≥ 20 weeks
- 1541 (34.5%) AMA vs 2928 (65.5%) non-AMA
- AMA: weekly BPP starting at 36 weeks, planned delivery at 41 weeks, or sooner if indicated
- Lethal and chromosomal abnormalities excluded
- Stillbirth in AMA tested similar to non-AMA
  - 3.9 per 1000 vs. 3.4 per 1000, p = 0.799

Fox NS, Eur J Ob Gyn, 2013
Relative Risk of Stillbirth by Maternal BMI

Nonlinear dose-response analysis

Best fitting fractional polynomial

95% CI

Aune D, et al. JAMA, 2014
Antenatal Testing for Maternal Obesity and Stillbirth Risk

• Retrospective cohort study of 512 women, BMI > 40, antenatal testing in 2012
  1. Morbid Obesity alone
  2. Morbid Obesity + comorbidity
  3. Non-morbid obesity + comorbidity

• Group 1 decreased induction rate compared to 2 & 3 adjusted for age and race

• GA at delivery (39.3 vs 38.5 vs 37.1) (P<.001)
Antenatal Testing for Maternal Obesity and Stillbirth Risk

- Antenatal testing was associated with increased risk of induction and decreased gestational age at delivery in women with comorbidities.
- Was not able to determine whether antenatal testing decreases the stillbirth risk in morbidly obese women.
- No increase in “morbidity” as result of APT

Timing of Delivery Induction as an intervention?

'Aargh!! My back's just gone!!'
Perinatal Complications

• Pregnancies that continue beyond 39 weeks are associated with increased risks of:
  • Stillbirth
  • Meconium aspiration syndrome
  • Mechanical ventilation
  • Birth trauma
  • Neonatal seizures/ICH/ encephalopathy
  • Neonatal sepsis
  • UA pH ≤7/BE < -12
Maternal Complications

- Pregnancies that continue beyond 39 weeks are associated with increased risks of:
  - Cesarean delivery
  - Operative vaginal delivery
  - 3rd and 4th degree lacerations
  - Febrile morbidity
  - Hemorrhage
Induction and Cesarean Delivery: Common Wisdom

- Retrospective cohort studies
- Induction of labor prior to 41 weeks of gestation is associated with an approximately 2-fold higher risk of cesarean delivery in nulliparous women
EIOL vs. Expectant Management at 39 Weeks

10% decreased odds of cesarean in EIOL group

Cheng et al AJO 2012; Stock BMJ 2012
EIOL vs. Expectant Management at 39 Weeks: Perinatal Consequences

70% decreased odds of mec aspiration and mortality, respectively, in EIOL group

Cheng AJOG 2012; Stock BMJ 2012
**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 = 6,000
Use of Labor Induction and Risk of Cesarean Delivery: a Systematic Review and Meta-analysis

• 157 eligible RCTs (n =31,085)
• IOL vs expectant management
• CD 12%: RR 0.88, 95% CI 0.84–0.93
  • Initial cervical score, indication, method of induction did not alter the main result
• Stillbirth: RR 0.50, 95% CI 0.25–0.99
• NICU admission: RR 0.86, 95% CI 0.79–0.94
• No impact on maternal death

CMAJ 2014
Low Dose Aspirin (LDA)

• Anti-inflammatory effects
• Impacts endometrial vascularization and placentation (blood flow)
• Few maternal side effects
• Safe during pregnancy
• Widely available
• Inexpensive
Aspirin: Preeclampsia Prevention

Systematic review

- 39 trials included (45 excluded)
- 30,563 women
- 28,802 women – LDA vs placebo
- Preeclampsia, Preterm birth, SGA, fetal or neonatal death

Duley 2001; BMJ; 322:329
Aspirin: Preeclampsia Prevention

• Preeclampsia:
  • 15% reduction (0.85)
  • # needed to treat – 100

• Preterm birth:
  • 14% reduction (0.92)
  • # needed to treat 72

• Fetal / Neonatal death
  • 14% reduction (0.86)
  • # needed to treat - 250

Duley 2001;BMJ;322:329
NICHD Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be (nuMoM2b)

- Pregnancies complicated by:
- Preterm birth
- Preeclampsia / gestational high BP
- Fetal growth restriction
- Stillbirth
- Overlap in pathophysiology of APO
nuMoM2b

• Large prospective observational cohort
• 10,000 singleton pregnancies
• Multi-center (8 sites)
  • Case Western Reserve University
  • Columbia University/Christiana Hospital
  • Indiana University
  • University of Pittsburgh
  • Northwestern University
  • University of California – Irvine
  • University of Pennsylvania
  • University of Utah
  • RTI International – DCC
nuMoM2b Protocol

Comprehensive clinical and biospecimen data

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

Visit 1
6 – 13 6/7 weeks

Visit 2
16 – 21 6/7 weeks

Visit 3
22 – 29 6/7 weeks
Sleep Position: A Possible Intervention?

• Sydney Stillbirth Study
  • Case - control: 103 women with stillbirth and 192 controls
  • Suspected IUGR (AOR 5.5) and supine sleeping in the last month (AOR 6.26) most strongly associated with stillbirth
  • SGA < 10\textsuperscript{th} percentile overrepresented in the supine sleepers, associated with late - pregnancy stillbirth

nuMoM2b Sleep Sub-study

- Prospective study
- 10,000 singleton pregnancies
- Questionnaires / Clinical data
- Sleep position questions
- 3,630 singleton pregnancies
- Objective measures of sleep disordered breathing (SDB) with Embletta Gold device
nuMoM2b Sleep Sub-study

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

• SDB leads to pathophysiology
  • Increased sympathetic tone
  • Oxidative stress
  • Systemic inflammation
  • Insulin resistance
  • Hyperlipidemia
nuMoM2b Sleep Sub-study

- SDB in early and mid-pregnancy
- Preeclampsia
  - Early aOR 1.94 (95% CI 1.07–3.51)
  - Mid aOR 1.95 (95% CI 1.18–3.23)
- Hypertensive disorders of pregnancy
  - Early aOR 1.46 (95% CI 0.91–2.32)
  - Mid aOR 1.73 (95% CI 1.19–2.52)
- GDM
  - Early aOR 3.47 (95% CI 1.95–6.19)
  - Mid aOR 2.79 (95% CI 1.63–4.77)
SCRN: Infection Ongoing Research

- Microbiome / molecular assessment of infection in stillbirth
- SCRN samples
  - Fetal tissue: cases
  - Placenta: cases and controls
- Viral discovery
  - Unbiased high throughput sequencing
  - Single plex PCR
- Bacterial discovery
  - Bacterial 16S rRNA gene pyrosequencing (454)
  - Real time PCR
THANK YOU!

Stillbirth Collaborative Research Network

[Image of group photo with logos for Stillbirth Collaborative Research Network and NIH]