Stillbirth

Laura Whisler, M.D.
University of Kansas – Wichita
Department of OB-Gyn
ACOG Objectives

- Describe the possible causes of fetal death.
- Interpret the results of diagnostic tests to determine the etiology of fetal death.
- Select and perform the most appropriate procedure for uterine evacuation based on considerations of gestational age and maternal history.
- Describe the grieving process associated with pregnancy loss and refer patients for counseling as appropriate.
- Counsel patients about recurrence risk of fetal death.
Background

- 1 in 160 deliveries in the U.S is complicated by stillbirth
- Definition not completely uniform
  - 20 weeks or greater OR
  - 350 grams or more (50%ile at 20 wks)
  - WHO – death prior to the complete expulsion of extraction from its mother of a product of conception, irrespective of the duration of pregnancy.
Epidemiology (U.S.)

- Stillbirth rate is higher than the neonatal death rate
- Stillbirth rate is lower than the infant mortality rate
- Antepartum >> Intrapartum fetal death
- More common for fetal death to be unexplained

2005 – 6.2/1,000 deliveries
- Early (20-27.6) 3.2/1,000 (stable since 1990)
- Late (≥ 28) 3.1/1,000 (29% decline)

50% of LATE fetal deaths occur at term
# Risk Factors for Stillbirth

## Table 1. Commonly Reported Maternal Risk Factors and Causes for Stillbirth

<table>
<thead>
<tr>
<th>Developed Countries</th>
<th>Developing Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital and karyotypic anomalies</td>
<td>Obstructed and prolonged labor and associated asphyxia, infection, and birth injury</td>
</tr>
<tr>
<td>Growth restriction and placental abnormalities</td>
<td>Infection especially syphilis and gram-negative infections</td>
</tr>
<tr>
<td>Medical diseases such as diabetes, systemic lupus erythematosus, renal disease, thyroid disorders, and cholestasis of pregnancy</td>
<td>Hypertensive disease and complications of preeclampsia and eclampsia</td>
</tr>
<tr>
<td>Hypertensive disease and preeclampsia</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Infection such as human parvovirus B19, syphilis, streptococcal infection, and listeria</td>
<td>Poor nutritional status</td>
</tr>
<tr>
<td>Smoking</td>
<td>Malaria</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>Sickle cell disease</td>
</tr>
</tbody>
</table>

Risk Factors for Stillbirth

Race

- Non-Hispanic black women – 11.25/1,000 (1/87)
  - Higher rates even if adequate PNC
  - Increased rates of comorbidities (DM, htn, abruption, PROM)
- White (1/202), Hispanic (1/183), Asian and Native American stillbirth rates are all less than 6/1,000
- Etiology frequency also affected by race
  - White women – placental abruption
  - South Asian and black women - IUGR
Risk Factors for Stillbirth

- Socioeconomics
  - Low-Income countries – 9-34/1,000
    - ½ in labor and delivery
  - High-Income countries – 3.1/1,000
  - 98% of stillbirths occur in low and middle-income countries
## Risk Factors for Stillbirth

### Table 2. Estimates of Maternal Risk Factors and Risk of Stillbirth

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Estimated rate of stillbirth</th>
<th>OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnancies</td>
<td></td>
<td>6.4/1000</td>
<td>1.0</td>
</tr>
<tr>
<td>Low-risk pregnancies</td>
<td>80%</td>
<td>4.0–5.5/1000</td>
<td>0.86</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>6%–10%</td>
<td>6–25/1000</td>
<td>1.5–2.7</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>5.8%–7.7%</td>
<td>9–51/1000</td>
<td>1.2–4.0</td>
</tr>
<tr>
<td>Severe</td>
<td>1.3%–3.3%</td>
<td>12–29/1000</td>
<td>1.8–4.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated with diet</td>
<td>2.5%–5%</td>
<td>6–10/1000</td>
<td>1.2–2.2</td>
</tr>
<tr>
<td>Treated with insulin</td>
<td>2.4%</td>
<td>6–35/1000</td>
<td>1.7–7.0</td>
</tr>
<tr>
<td>SLE</td>
<td>&lt;1%</td>
<td>40–150/1000</td>
<td>6–20</td>
</tr>
<tr>
<td>Renal disease</td>
<td>&lt;1%</td>
<td>15–200/1000</td>
<td>2.2–30</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>0.2%–2%</td>
<td>12–20/1000</td>
<td>2.2–3.0</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>1%–5%</td>
<td>18–40/1000</td>
<td>2.8–5.0</td>
</tr>
<tr>
<td>Cholestasis of pregnancy</td>
<td>&lt;0.1%</td>
<td>12–30/1000</td>
<td>1.8–4.4</td>
</tr>
<tr>
<td>Smoking &gt;10 cigarettes</td>
<td>10%–20%</td>
<td>10–15/1000</td>
<td>1.7–3.0</td>
</tr>
</tbody>
</table>
# Risk Factors for Stillbirth

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Estimated rate of stillbirth</th>
<th>OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (prepregnancy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI 25–29.9 kg/m²</td>
<td>21%</td>
<td>12–15/1000</td>
<td>1.9–2.7</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>20%</td>
<td>13–18/1000</td>
<td>2.1–2.8</td>
</tr>
<tr>
<td>Low educational attainment (&lt;12 y vs. 12 y+)</td>
<td>30%</td>
<td>10–13/1000</td>
<td>1.6–2.0</td>
</tr>
<tr>
<td>Previous growth-restricted infant (&lt;10%)</td>
<td>6.7%</td>
<td>12–30/1000</td>
<td>2–4.6</td>
</tr>
<tr>
<td>Previous stillbirth</td>
<td>0.5%–1.0%</td>
<td>9–20/1000</td>
<td>1.4–3.2</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twins</td>
<td>2.7%</td>
<td>12/1000</td>
<td>1.0–2.8</td>
</tr>
<tr>
<td>Triplets</td>
<td>0.14%</td>
<td>34/1000</td>
<td>2.8–3.7</td>
</tr>
<tr>
<td>Advanced maternal age (reference &lt;35 y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–39 y</td>
<td>15%–18%</td>
<td>11–14/1000</td>
<td>1.8–2.2</td>
</tr>
<tr>
<td>40 y+</td>
<td>2%</td>
<td>11–21/1000</td>
<td>1.8–3.3</td>
</tr>
<tr>
<td>Black women compared with white women</td>
<td>15%</td>
<td>12–14/1000</td>
<td>2.0–2.2</td>
</tr>
</tbody>
</table>

*OR of the factor present compared to the risk factor absent.
Causes of Stillbirth

Stillbirth Collaborative Research Network Writing Group (JAMA 2011)

2006-2008

N=500 women who consented to postmortem examination

Possible or probable cause of death was found in 76.2%

- Obstetric complications (multiples, abruption, preterm birth) 29.3%
- Placental disease 23.6%
- Fetal genetic or structural abnormalities 13.7%
- Maternal or fetal infection 12.9%
- Umbilical cord abnormalities 10.4%
- Hypertensive disorders 9.2%
- Other maternal medical conditions 7.8%
Causes of Stillbirth

- Variations by Gestational Age
  - 24-27 wga – infections (19%), abruption (14%), fetal anomalies (14%)
  - After 28 wga – unexplained, IUGR, abruption
Unexplained Stillbirth

- Reported to account for 25-60% of all fetal deaths
  - Range is a reflection of variable evaluations

- Term stillbirths are more likely to be unexplained

  - n=196
  - Independent Risk Factors (OR)
    - Prepregnancy weight >68kg (2.9)
    - Birth weight ratio 0.75-0.85 (2.77)
    - Parity ≥3 (2.01)
    - Primiparity (1.74)
    - Low socioeconomic status (1.59)
Causes of Stillbirth

- **IUGR** – risk of stillbirth 3-7 times increased
- **Placental Abruption** – 10-20% of all stillbirths
  - Highest risk when >50% or the central placenta is affected
- **Infection**
- **Chromosomal abnormalities**
  - **Hsu, et al** – n=823
    - 6.3% had chromosomal abnormality
    - 0.7% of live births
    - Trisomy 18, 13 and 21, sex chromosome aneuploidy and unbalanced translocations
Causes of Stillbirth

- Congenital anomalies – 15-20% of stillbirths have a major malformation
  - Abdominal wall defects, NTD, Potter syndrome, achondroplasia, amniotic band

- Fetomaternal hemorrhage – up to 5%
  - Associated with abruption, vasa previa, chorioangioma, choriocarcinoma, trauma, ECV, amnio

- Umbilical cord complications

- Hydrops fetalis

- Arrhythmia
Causes of Stillbirth

- Platelet alloimmunization
- Placental disorders
  - Abruption, vasaprevia, placental infection, neoplasms, structural or vascular malformations, infarction, mosaicism
- Uterine conditions - Rupture
Evaluation of Stillbirth

- Obstetric history – exposures, family history, comorbidities

- Maternal Laboratory Evaluation
  - Kleihauer-Betke
  - Urine Toxicology
  - CBC
  - Serological testing for syphilis, CMV, Toxo, Parvo.
  - Hemoglobin A1C
  - Antibody Screen
  - APLS
  - TSH
Evaluation of Stillbirth

Kleihauer-Betke Test

- % fetal RBC in maternal circulation
- Fetal erythrocytes contain Hbg F, which is more resistant to acid elution than Hbg A.
- After exposure to acid only fetal cells remain
- Fetal cells X maternal blood volume / Total RBCs counted = FML (mL)
Evaluation of Stillbirth

APLS

Inherited Thrombophilias

- A personal history of venous thromboembolism that was associated with a nonrecurrent risk factor (e.g., fractures, surgery, and prolonged immobilization). The recurrence risk among untreated pregnant women with such a history and a thrombophilia was 16% (odds ratio, 6.5; 95% confidence interval, 0.8–56.3) (55).
- A first-degree relative (e.g., parent or sibling) with a history of high-risk thrombophilia.

Box 2. Clinical Criteria for Diagnosis of Antiphospholipid Syndrome

1. Vascular thrombosis
   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ, or

2. Pregnancy morbidity
   a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
   b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia, or features consistent with placental insufficiency, or
   c) Three or more unexplained consecutive spontaneous pregnancy losses before the 10th week of pregnancy, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Evaluation of Stillbirth

Fetal Laboratory Studies

- **Karyotype (FISH if culture fails)**
  - Amniotic fluid, umbilical cord, fetal tissue or placenta
  - Amnio or CVS has highest yield (80-90% vs 10-30%)
  - After delivery the most viable tissue is 1X1 cm segment of umbilical cord closest to the placenta
  - Can also obtain fetal cartilage (costochondral junction or patella) or 1.5cm umbilical cord segment
  - Fresh tissue sample medium – Hanks balanced salt solution or sterile saline solution
  - 2 samples ideal – fascial and umbilical cord

- **Microarray**
  - Does not require dividing cells
Evaluation of Stillbirth

- n=1477
- Autopsy identified the cause of death in 46%
- New information in 51%
- Estimated recurrence risk adjusted in 40%

Autopsy should include a gross and microscopic exam, photographs, X-rays, fetal culture (lung), histology (placental and fetal tissue)

Estimating time of death
- >6hrs – brown or red cord and ≥1cm desquamation
- >12hrs – Desquamation of face, back, abdomen
- >18hrs - ≥5% or ≥2 body zones
- >24hrs – skin brown or tan
- >2wks-Mummification (deep brown tissues, leathery skin)

Histology can guide this
Evaluation of Stillbirth

Fetal Inspection

Inspect fetus and placenta:
- Weight, head circumference, and length of fetus
- Weight of placenta
- Photographs of fetus and placenta
- Frontal and profile photographs of whole body, face, extremities, palms, and any abnormalities
- Document finding and abnormalities

Placental Pathology
Evaluation of Stillbirth

Alternatives to Autopsy
- Placental evaluation and external exam (measurements, X-ray, photographs)
- Above plus selected biopsies (evaluate fetal infections)
- Above plus internal examination (organs left in the body)
- Head Sparing Autopsy
- MRI
- Ultrasound
Delivery of a Stillbirth

- **Third Trimester**
  - Misoprostol 25-50 mcg vaginally every 4hrs followed by oxytocin

- **Second Trimester**
  - Misoprostol 200-400 mcg vaginally every 4-12 hours
  - Mean expulsion time is 10-11 hours
  - D&E – limits autopsy

- **Placenta Previa – Cesarean**

- **Previous CD**
  - 2nd trimester vaginal misoprostol is supported with previous LTCS 400mcg every 6 hours
  - 3rd Trimester consider foley balloon
  - Classical Incision – no definitive stance by ACOG
Recovery and Support

- Clear communication of test results
- Referral to bereavement counselor, religious leader, support groups or mental health professional may be indicated.
Prevention of Stillbirth

- Bhutta et al (Lancet 2011)
- Folic Acid
- Malaria prevention
- Syphilis detection and treatment
- Detection and management of hypertension
- Detection and management of diabetes
- Detection and management of IUGR
- Post-term pregnancy induction ≥41 wks
- Skilled birth attendant
- Availability of basic and comprehensive emergency obstetric care
Prevention of Recurrent Stillbirth

- Thorough history
- Prenatal diagnosis of fetal anomalies
- Kick counts (28wks)
- Antepartum fetal surveillance
  - 1-2 weeks prior to the gestational age of the previous stillbirth and by 32-34 wga
  - If patient has a prior IUGR pregnancy a growth sono should be performed around 28 wga
- Timing of delivery
  - Avoid scheduled delivery before 39 weeks in a currently uncomplicated pregnancy
  - Consider elective delivery at 39 weeks
PB 102 Summary

Level A

- Recurrence risk in low-risk and prior unexplained stillbirth is 7.8-10.5/1,000 (most before 37wks)
- The most prevalent risk factors are non-Hispanic black race, nulliparity, AMA and obesity
- Risk of subsequent stillbirth is 2X as high for women with a prior IUGR live-born before 32 weeks than for women with a prior stillbirth
- Amnio for fetal karyotype has the highest yield

Level B

- In 2nd trimester D&E and labor induction can be offered
- IOL with vaginal misoprostol is safe in patients with a prior LTCS before 28 weeks

Level C

- The most important tests in evaluating stillbirth are fetal autopsy; placental and cord exam and karyotype evaluation
Questions