Stillbirth: clinical challenges, ongoing research, and future opportunities

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USA: 6.2 million pregnancies/yr

Abotions 22%
Births 62%
Fetal deaths 16%

Death prior to the complete expulsion or extraction from its mother of a product of human conception, irrespective of the duration of pregnancy and which is not an induced termination of pregnancy.
**U.S. Reporting requirements**

Reporting fetal deaths of ≥ 350 grams or if weight is unknown, ≥ 20 completed weeks gestation or more

(The reporting requirement in the U.S. by the Model Law, 1992 Revision)

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**Stillbirth rates**

- One of the most common adverse pregnancy outcomes (1 in 200 pregnancies)
  - 26,000 stillbirths every year (2003 data)
- US Stillbirth rate: 6.2 deaths per 1000 live births
  - mortality due to prematurity and SIDS combined
  - infant deaths in US
  - 1/2 of all perinatal mortality
- SB rates/1000 births
  - Blacks: 12.1 vs. Whites: 5.5
- 50% - undetermined cause of death

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**US Vital statistics**

- Infant Mortality
- Stillbirth

<table>
<thead>
<tr>
<th>Year</th>
<th>Infant Mortality</th>
<th>Stillbirth</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>2002</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
Maternal disease

- ~10% of SB associated with maternal conditions
- Late fetal deaths are associated with maternal medical conditions that are potentially preventable

Maternal Disease: Current Stillbirth Rates

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated Stillbirth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnancies</td>
<td>6-7/1,000</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>10/1,000</td>
</tr>
<tr>
<td>PIH/mild preeclampsia</td>
<td>10/1,000</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>20/1,000</td>
</tr>
<tr>
<td>Eclampsia/HELLP Syndrome</td>
<td>50/1,000</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>5-10/1,000</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>6-10/1,000</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>20/1,000</td>
</tr>
</tbody>
</table>

Maternal Disease: Current Stillbirth Rates

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated Stillbirth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>18/1,000</td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>100/1,000</td>
</tr>
<tr>
<td>Mild renal insufficiency</td>
<td>15/1,000</td>
</tr>
<tr>
<td>Severe renal insufficiency</td>
<td>200/1,000</td>
</tr>
<tr>
<td>Stable treated hyperthyroidism</td>
<td>10/1,000</td>
</tr>
<tr>
<td>Uncontrolled thyrotoxicosis</td>
<td>125/1,000</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>10/1,000</td>
</tr>
<tr>
<td>Cholestasis of pregnancy</td>
<td>12-30/1000</td>
</tr>
</tbody>
</table>

Simpson, 2002
Stillbirth - Hypertension

- Prior to modern OB care, hypertensive disorders accounted for 20-40% of all SB
- In recent years, 4-9% of all SB occur in hypertensives
- Preeclampsia rather than hypertension is the major risk factor
  - cHTN without superimposed PE = general pop = 5/1000
  - PIH: 9/1000
  - Eclampsia: 18/1000
  - Severe PE without HELLP: 21/1000
  - HELLP: 50/1000

Hypertension

- Pathways to SB include:
  - Placental insufficiency
  - Placental infarction
  - Abruption
  - Fetal-maternal hemorrhage
  - SGA/IUGR
- Abruption highest in eclampsia

Hypertension

- Accurate dating, frequent prenatal visits for evaluation of medical complications, antenatal fetal testing, and timely delivery
- Lack of data antihypertensive therapy decreases the risk of SB
- Umbilical artery Dopplers valuable surveillance tool for pregnancies c/o htn and IUGR
  - Highly predictive of SB with all cases showing absent end-diastolic flow
- Expectant mgmt in HELLP syndrome: SB rate
- Prevalence, absolute risk of SB
Diabetes

- Prior to modern OB care, 50% of all diabetic pregnancies ended in SB
- GDM SB rate = general population
- Type 1 and 2 DM: SB risk of 2nd and 3rd trimester
- 3% of all SB
  - Intensive surveillance program
  - SB rate pre-gestational DM~ GDM ~ general population

Diabetes

- Subsequent pregnancies in women with a previous SB: 4 fold increase in glucose intolerance or GDM
- Unexplained SB: 18% abnormal glucose tolerance testing but did not meet the criteria for GDM
- Some cases of unexplained SB?
  Undetected maternal DM

Diabetes

- Mechanism of SB is unknown
- Majority of SB occur in third trimester:
  - poor glycemic control
  - complications of macrosomia, polyhydramnios, IUGR, and preeclampsia
- Alterations in fetal carbohydrate metabolism and uteroplacental insufficiency secondary to vascular disease
- Maintenance of euglycemia, antepartum fetal surveillance, timely delivery decrease SB
Antiphospholipid syndrome (APS)

- Autoimmune disorder
  - Antiphospholipid antibodies
  - Clinical events: thrombosis, recurrent pregnancy loss after 14 weeks, autoimmune thrombocytopenia
- Fetal death associated with growth restriction/placental insufficiency
- Placental pathology: if thrombosis, infarction, or vascular damage, order LAC and ACA
- Treatment: heparin and low dose ASA improves obstetric outcome

Thrombophilias

A heterogeneous group of conditions that predispose individuals to (venous) thromboembolism

Thrombophilia

- Four-fold increased risk of stillbirth
- Preeclampsia and IUGR
- Alterations of placental function from infarction and abruption
- Thrombotic damage in placenta
- Complications of fetal hypercoagulability, intrauterine stroke, SB
Thrombophilias: Prevalence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gen Pop</th>
<th>Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>5-9%</td>
<td>20-40%*</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>3%</td>
<td>6-15%</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.3%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>0.2%</td>
<td>1-2%</td>
</tr>
<tr>
<td>AT III deficiency</td>
<td>0.07%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hyperhomocystinemia</td>
<td>5%</td>
<td>5-10%</td>
</tr>
</tbody>
</table>

* Prevalence lower in Latin, African and Asian Americans

Thrombophilias and Pregnancy Loss: Meta-analysis

- Medline 1975 – 2002
- 31 studies
- Mostly retrospective
- Moderate-high quality

Rey et al., Lancet 2003;361:901
Factor V Leiden
Prospective Obstetric Outcome

- Prospective cohort - MFMU
- 5,188 women in early pregnancy
- Factor V Leiden – 134 (2.7%)
  - No increase in VTE!
  - 4 VTE – all testing negative
### Factor V Leiden

**Prospective Obstetric Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Carriers</th>
<th>Controls</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Loss</td>
<td>5.97%</td>
<td>5.49%</td>
<td>1.1 (0.5 - 2.2)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>3.73%</td>
<td>2.99%</td>
<td>1.3 (0.5 - 3.0)</td>
</tr>
<tr>
<td>Abruption</td>
<td>0</td>
<td>0.65%</td>
<td>0.9 (0.4 – 2.1)</td>
</tr>
<tr>
<td>SGA (&lt; 10%)</td>
<td>9.7%</td>
<td>10.8%</td>
<td>0.9 (0.5 – 1.6)</td>
</tr>
</tbody>
</table>

Dizon-Townson, Obstet Gynecol, 2005

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### Thrombophilia and Adverse Pregnancy Outcomes

- Apparently conflicting results
  - Retrospective vs. prospective
- Most women with thrombophilias:
  - Normal pregnancy outcome
- “Two-hit” hypothesis
- Thrombophilia and fetal death (or thrombosis) is different than thrombophilia alone

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### Thrombophilias and Pregnancy Loss

**Thromboprophylaxis**

- Multicenter RCT: One prior loss > 10 wks
- Thrombophilia
  - Factor V Leiden
  - Prothrombin
  - Protein S deficiency
- 5 mg folic acid preconception
- Randomization
  - Low dose aspirin (100 mg QD) n=80 or
  - Enoxiparin (40 mg QD at 8 weeks) n=80

Gris et al., Blood 2004;103:3695
Thrombophilias and Pregnancy Loss

LMWH - OR for live birth: 15.5 (7 – 34)
Similar results for each thrombophilia
Lower birth weight in LDA group

SLE

- Reproductive age women
- < 1% of pregnancies
- SB rate= 150/1000 births (12 series published prior to 1990)
- Improved rate = 40/1000 births
  - Better understanding of pathophysiology
  - Earlier diagnosis
  - Improved interventions and treatment
- Conception during disease quiescence better than during active lupus flare

Obesity

- Prevalence of overweight and obesity is rapidly rising in developed countries
  - US- 1/3 of pregnant pop with BMI > 25
- SB rate= 15-20/1,000 births
- Increasing pre-pregnancy BMI is associated with stillbirth.
- Pregnancy weight gain is not associated with stillbirth.
- Pre-gestational DM, GDM, chronic hypertension, preeclampsia occur more frequently
- Mechanisms for BMI related increase in SB is unknown
Proportion of SBs “due to” infection

- Sweden: Infection 15%
- Quebec: Infection 9%

Fretts, ObGyn 1992; 79:35-9

Proportion of SBs “due to” Infection by Gestational Age

- <28 weeks (n=43): 19%
- 28-36 weeks (n=62): 8%
- ≥37 weeks (n=48): 2%

Fretts, ObGyn 1992; 79:35-9

Infections & Stillbirth

“Likely to cause”
- Parvovirus
- Cytomegalovirus
- Treponema pallidum
- Toxoplasma gondii
- Listeria monocytogenes

“Purported to Cause”
- Ureaplasma urealyticum
- Mycoplasma hominis
- Chlamydia trachomatis
- HIV
- Many others

Gibbs, Ann Arbor, 2002
Viral infections

- Uncertain proportion of SB
- Lack of a systematic approach
- Difficult to culture
- Positive viral serologic result or presence viral DNA or RNA in fetal/placental tissue does not prove causation
- Parvovirus B19 and Coxsackie viruses most important
- Increased use of molecular diagnostic technology (DNA and RNA PCR) increase diagnosis
- Coxsackie viruses - cross the placenta - villous necrosis, inflammatory cell infiltration
  - Calcific panniculitis/ hydrops/ cardiovascular defects

Parvovirus B19

- 8% of stillbirths by PCR, not serology/culture in Swedish survey (Skjoldebrand 2000)
- < 1% of all SB in U.S. (Goldenberg 2003)
- Proportion of SB underestimated
- Most common clinical presentation: erythema infectiosum or fifth disease, ("slapped cheek" rash).
- Crosses placenta - attacks fetal erythropoietic tissue severe fetal anemia - nonimmune hydrops
  (Young 2004)
- Directly attacking fetal cardiac tissue → myocardial damage

Cytomegalovirus (CMV)

- Most common congenital viral infection
- 1% of pregnant women acquire primary CMV during pregnancy
- Highest rate of transmission to fetus, most severe consequences, occur with primary maternal infection.
- Placental damage → IUGR
- Association with stillbirth remains controversial (Gibbs 2002, Goldenberg 2003)
Cytogenetics
- Chromosome anomalies in 6-12%
  (10 times the rate in liveborn)
- Rate underestimated: failure to culture cells
- Proportion of chro abnl / SB with structural malformations
- 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
  - congenital anomalies or hydrops present

Genetics & Stillbirth
- Mendelian disorders as a cause of stillbirth:
  - Autosomal recessive disorders
  - X-linked disorders
  - Confined placental mosaicism

Autosomal Recessive Metabolic Disorders Known to Cause Stillbirth
- Hemoglobinopathies:
  - α Thalassemia
- Amino acid disorders:
  - Glutaric aciduria, Type II
- Peroxisomal Disorders:
  - Zellweger Syndrome
- Thrombophilias - homozygous or compound heterzygous
- Storage Diseases:
  - Sialodosis
  - Galactosialodosis
  - Sialic acid storage disease
  - Nieman Pick, AC
  - I Cell Disease
  - GMI, gangliosidosis, Type I
  - Gaucher’s Disease

Wapner & Lewis, Sem Perinatol, 2002
Umbilical cord accidents & SB

- 15% of SB may be due to UCA
- Possible mechanisms:
  - Cessation of blood flow
  - Intermittent disruption of blood flow
  - Fetal blood loss and disruption of flow
  - Cord entanglement
  - Cord abnormalities
  - Uterine ischemia
- Demonstrate cord occlusion, hypoxic tissue injury on autopsy, and exclude other accepted causes of stillbirth.

Fetal-Maternal Hemorrhage

- 3 - 14% of all stillbirths
  (Owen 1989; Laube 1982; Petersson 2002)
- Volume of blood transfused ~ 50% - 75% of total fetal-placental blood volume
- Significant FMH: external cephalic version, cesarean section, manual removal of the placenta, placental abruption and abdominal trauma
- Reliable method for identification and quantification of FMH prior to labor induction
- Evidence of hypoxia and anemia on autopsy

Evaluation of Stillbirth: Why?

- Facilitates grieving process
- Essential to counsel regarding recurrence risks
- Sporadic cause - reassurance
- Improve understanding to facilitate therapeutic measures
- Decreased proportion of unexplained SB with systematic evaluation
**Evaluation of stillbirth**

- CONTROVERSIAL
- Difficulty to attributing to single etiology
- Investigation into previously unrecognized causes limited
- Emotionally charged event - different families and cultures varied levels of comfort with autopsy or genetic testing
- Cost of testing

**Stillbirth Evaluation**

- Involve:
  - Maternal-Fetal Medicine specialists
  - Neonatologists
  - Pathologists
  - Geneticists
- Parental counseling with findings

**Recommended assessment of IUFD (ACOG Techin Bull #176)**

- Thorough physical exam, notes, photographs
- Clinical geneticist
- Autopsy, placental examination
  - Placental pathology: if thrombois, infarction, or vascular damage, order LAC and ACA
- X-rays (whole body A-P)
- Karyotype (~6% abN, 25% with malformation)
- Detailed obstetrical and family history
**Recommended assessment of IUFD (ACOG Tech Bull #176)**

- Kleihauer-Betke
- glucose (if 1 hour GTT not available)
- CBC with platelets
- indirect Coombs
- VDRL
- urine toxicology

**Autopsy**

- Single most useful step in evaluation
- 55% of cases the autopsy cause of death differed from the fetal death record (JAMA 1989)
- Birth defects and morphologic abnormalities - genetic or developmental abnormalities
- Confirm infection, anemia, hypoxia, and metabolic abnormalities
- Limited use by cost, lack of trained pathologists, discomfort by physicians and patients in discussing or having the procedure
- Partial autopsy or post-mortem MRI (Woodward)

**Placental, membranes, umbilical cord evaluation**

- Infection, genetic abnormalities, anemia, and thrombophilias
- Trained pathologists
- Scientific, systematic evaluation
- Increasingly advised for medico-legal purposes in all cases of adverse Perinatal outcome (e.g. PTB, SB)
Karyotyping

- Postnatal testing: failure rate of 24%–27%; influenced by delivery-to-sampling interval, not gestational age or type of tissue sampled. 
  - Mueller 1983; Kyle 1996
- Amniocentesis: failure rate = 8%
  - Brady 1991

Karyotyping

- Trained pathologist- tissues for karyotype after gross evaluation of the fetus and placenta.
- DO NOT put placental/fetal tissues in formalin

Obtain consent from parents for cytologic specimens:

- Obtain cytologic specimens with sterile techniques and instruments.
- Acceptable cytologic specimens (at least one):
  - Amniotic fluid obtained by amniocentesis at time of prenatal diagnosis of demise; particularly valuable if delivery is not expected imminently
  - Placental block (1 × 1 cm) taken from below the cord insertion site on the unfixed placenta
  - Umbilical cord segment (5.5 cm)
  - Internal fetal tissue specimen, such as costochondral junction or patellar; skin is not recommended.
- Place specimens in a sterile tissue culture medium of lactated Ringer’s solution and keep at room temperature when transported to cytology laboratory.
**Infection workup**

- Autopsy and histologic evaluation of the placenta, membranes and umbilical cord
- Pathologist: obtain cultures and nucleic acid specimens (bacteria or viruses) based on histology
- Routine cultures or serology – controversial
- Parvovirus serology
- Syphilis screening
- Serology for “TORCH” (toxoplasmosis, rubella, cytomegalovirus, herpes simplex) - low yield

**Fetal-maternal hemorrhage**

- Kleihauer-Betke test (KBT)
  - Elution of adult hemoglobin (HbA) from adult red cells, more acid-resistant fetal hemoglobin (HbF) remains intact in fetal RBC
  - Remaining hemoglobin is subsequently visualized by staining with erythrosin
- Flow cytometry
  - May be more accurate
  - Used by some centers
Pregnancy after stillbirth

- Difficult for couple
  - Anxiety, failure, personal guilt, apprehension
  - Lack of closure - cause of stillbirth remains unknown (50%), never counseled postpartum
- Difficult for clinicians to optimally counsel, evaluate and manage
- Very little is known about pregnancy after experiencing stillbirth

Recurrence risk

- Recurrence risk 2 to 10 fold in next pregnancy
  Greenwood, 1994; Simoff, 1993
- Earlier losses - higher risk of subsequent adverse outcome
  - 95 women with fetal death 13-24 weeks
    - 40% PTD
    - 5% stillbirth
    - 6% neonatal death
  Goldenberg, Obstet Gynecol, 1993
Recurrence risk

- Swedish national database: 410,000 deliveries
  - Live birth of growth restricted term infant
    2 fold increased risk of SB in next pregnancy
  - Live birth of growth restricted preterm infant
    5 fold increased risk of SB in next pregnancy

Surkan, 2004

Recurrence risk

- Cross sectional study, Finnish birth registry
- SB > 24 weeks or fetal weight > 500 grams
- Excluded multiple gestations, structural and chromo abnl, IDDM, preeclampsia, isoimmunization, uterine anomalies
- Cause of death classified
  - 29% of cases unknown cause of death

Heinonen, Birth, 2000

Pregnancy complications of women with hx of previous SB

- No recurrence of stillbirth
- Placental abruption (5.4% vs 0.7%)
- Cesarean delivery (30.4% vs. 13.4%)
- Preterm delivery (13% vs. 5.2%)
- Low birth weight infants (12% vs. 3.6%)
- Hx of stillbirth increased adverse pregnancy outcome

Heinonen, Birth, 2000
Recurrence risk

- Missouri maternally linked cohort data 1978-97
- 400,000 women with info on 1st and 2nd preg
- SB risk 5-fold with prior SB
  - OR= 4.7, 95% CI 3.3–6.6
  - 22.7/1000 vs. 4.7/1,000
- Recurrence rate was 2.6 fold higher for African-Americans compared to whites
  - 35.9/1,000 vs. 19.1/1,000

Recurrence risk: Summary

- Recurrence risk is 2-10 fold increased
  - Depends on
    » Etiology of prior SB
    » Presence of FGR
    » GA of prior SB
    » Race

Clinical: Risk Factors for Stillbirth

- Previous pregnancy outcomes
- Advance maternal age
- Black race
- Maternal obesity (prepreg BMI > 30 kg/m2)
- Post dates
- Smoking
- Maternal medical disease
- Fetal growth impairment
- Infertility
Maternal age and risk of stillbirth in U.S.

- SB risk at 37 to 41 weeks:
  - 35-39 yo
    - 1 in 382 ongoing pregnancies
    - RR= 1.32 (95% CI 1.22, 1.43)
  - > 40 yo
    - 1 in 267 ongoing pregnancies
    - RR= 1.88 (95% CI 1.64, 2.16)

- Medical disease, parity, race/ethnicity controlled

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

Reddy, AJOG, 2006
Fetal spleen

Thorough medical and obstetric history
Fetal autopsy
Placental evaluation
Karyotype
Indirect Coombs’
Serologic test for syphilis
Screen for fetal-maternal hemorrhage (Kleihauer-Betke or other)
Toxicology screen
Parvovirus serology

AJOG, 2007
Tests that may be useful in some cases
- Lupus anticoagulant screen
- Anticardiolipin antibodies
- Factor V Leiden mutation
- Prothrombin G20210A mutation
- Screen for protein C, protein S, and antithrombin III deficiency

Tests of uncertain utility
- TSH
- Glycohemoglobin
- Bile acids
- TORCH titers
- Placental cultures
- Testing for other thrombophilias

Developing technology
- Comparative genomic hybridization
- Genome wide analysis (SNPs)
- Candidate gene mutations
- Confined placental mosaicism
- Nucleic acid based testing for infection
Genetics of Stillbirth

Cytogenetics
(6 – 12% of stillbirths)

Frequency of Cytogenetic Abnormalities may be higher:
- 40 – 50% of karyotypes fail
- Older series have lower resolution and will miss small defects
- Role of Copy Number Variants:
  Microdeletions / duplications

Molecular genetic technologies

DNA based analysis
- Non-viable tissues are amenable to analysis

CNV is a DNA segment (usually larger than 1 kb) present at an altered copy number in comparison with a reference genome
- Whole chromosome aneuploidy
- Segmental Aneuploidy
  - Deletions
  - Duplications
  - Copy number polymorphisms

Comparative Genomic Hybridization

Differential labeling of DNA
Reference (Normal Genomic) DNA
Test DNA from Patient

Denature and preanneal
Hybridize to normal chromosomes on slides

Ratio profile
excess of test deficiency of
DNA

Slide courtesy of Dr. Ron Wapner
**Single Nucleotide Polymorphisms - SNPs**

- Single nucleotide difference
  - Randomly present in 1 of 1,250 base pairs
- Occurs in > 1% of population
- Usually non-functional
- When it occurs in promoter region or exon, may have effect
- Databases exist with millions of polymorphisms

**Functional - may result in increased or decreased gene or protein activity**

**Non-Functional - Serves as a marker of chromosomal location or regions**
Prediction: Factors from prior SB

- Knowledge of cause — better estimation of individual recurrence risk, guides mgmt
  - Aneuploidy - 1% recurrence
  - Familial DiGeorge syndrome - 50% recurrence
  - Offer CVS or amnio

- Maternal medical disorders
  - Intervention pre-conception or early pregnancy improves outcome
  - Diabetes - poor early glucose control — congenital anomalies — stillbirth

First trimester screen

- NT, PAPP-A, β-hCG

PAPP-A: protease for insulin-like growth factor (IGF) binding proteins 4 and 5
- Low PAPP-A — IGF bp free IGF
- IGFs: regulation of fetal growth, trophoblast function

PAPP-A < 5th percentile at 10 weeks

- FASTER Study: risk of SB > 24 weeks
  - OR = 2.15 (1.11–4.15)
  - Low sensitivity (10.5%) and PPV (0.58)

Dugoff, AOG, 2004

First trimester screen

- PAPP-A < 5th percentile at 10 weeks
- SB hazard ratio: 9.2 (4.0, 21.4)
  - 46 fold increased risk of SB due to placental dysfunction (abruption, IUGR) independent of maternal characteristics.
  - Not associated with other causes of SB
  - PPV for placental causes of SB = 1.8%

- Free β-hCG not assoc with SB risk of any cause

Smith, JAMA, 2004
**Second trimester screen**

- MSAFP, hCG, uE3, inhibin-A
- AFP- major fetal oncotic protein
- Unexplained MSAFP- assoc SB
  - Defect in placentation
- β-hCG ~ SB risk

Waller, Epidemiology, 1993
Wenstrom, Obstet Gyencol, 1996
Spencer, Prenat Diagn, 2000

**PAPP-A and AFP**

- Low PAPP-A: 5th percentile for GA
- High AFP: top 5th percentile for GA
- Low PAPP-A not associated with high AFP
  - Different aspects of placental dysf.
- Low PAPP-A + high AFP= synergistic increase SB risk = OR 36.7 (95% CI= 8.0, 167)
- 32% delivered SGA infant

Smith, Obstet Gynecol, 2006

**Placental implantation: effects on uterine artery Doppler**

Slide courtesy of A. Ghidini
Ultrasounds and Doppler studies: Uterine artery doppler

- Abnormal studies at 22-24 weeks
- Increased rates of development
  - preeclampsia
  - fetal growth restriction
  - perinatal death

Papageorghiou, Journal of Mat-Fetal and Neonatal Med, 2002

Ultrasounds and Doppler studies: Fetal growth restriction

- Single largest category of conditions associated with stillbirth (43%)
- Majority of cases previously considered unexplained

Gardosi, BMJ, 2005

Serial growth scans

FGR: definitions

- EFW < 10th percentile
  (10% of population)
- EFW > 2 SD below mean
  (~ 3rd percentile)
- EFW < 5th percentile
  (most clinically applicable)
Factors affecting EFW

- Fetal weight is related to:
  - Number of fetuses (singleton vs twin)
  - Ethnicity/race
  - Parity
  - Fetal gender
  - Maternal height
  - Maternal weight
  - Paternal height
- Individualized or customized growth standard improves prediction of adverse preg outcome
  - FGR vs. small healthy infant

Gardosi, Seminars Perinat, 2004

Ultrasounds and Doppler studies:
Progression: < 32 weeks'

- Worsening FGR (AC <10 centile)
- Abnormal umbilical artery Doppler
- Abnormal MCA
- Abnormal venous doppler
- Abnormal antenatal testing (NST/BPP)
- Fetal death

Slide courtesy of A. Ghidini

Prediction: Ultrasounds and Doppler studies ACOG Recommendations

- Doppler velocimetry useful in pregnancies complicated by FGR (with or without HTN/preeclampsia)
- Multiple RCT and meta-analyses of Doppler:
  - reduction of perinatal mortality by 38%
  - reduction in perinatal morbidity
  - reduction in CS for fetal distress
- Use Doppler in conjunction with other tests of fetal well-being

ACOG Practice Bull. 2000
Alfirevic et al AJOG 1995
**Prediction: Antepartum testing**
- Hx of SB important risk factor, such patients should undergo APT (Freeman, 1985)
- Optimal time to start
  - 70,000 tests, 15,000 patients
  - 300 healthy women with previous SB confirmed by medical records
  - Probable cause in 50% - cord accident, abruption, PIH, perinatal infection, fetal anomalies
  - FHR testing in subsequent pregnancy

**Prediction: Antepartum testing**
- 1 recurrent SB
- Up to 1989 weekly CSTs, 1990 semiwkly NST/AFI
- 6.4% + APT (+ CST or BPP < 6)
  - No relationship between GA of previous SB and abnormal APT in subsequent pregnancies
- APT should begin at 32 weeks or later in healthy pregnant women with a history of SB (ACOG recommendations, 1999)

**Management of subsequent pregnancy: Initial visit**
- Detailed medical and obstetrical history
- Evaluation of prior loss
- Determine recurrence risk based on available information
- Discussion of risk of other obstetrical complications
- Discussion of importance of
  - Serum markers in first & second trimester
  - Monitoring of fetal growth
  - Fetal kick counts
  - Antepartum fetal testing
Pregnancy complications of women with hx of previous SB

- Placental abruption (5.4% vs 0.7%)
- Cesarean delivery (30.4% vs 13.4%)
- Preterm delivery (13% vs 5.2%)
- Low birth weight infants (12% vs 3.6%)
- Hx of stillbirth increased adverse pregnancy outcome
  - Impaired placental development and function
  - Compromised vasculature

Management of subsequent pregnancy

- First trimester sonogram for accurate dating
- Maternal serum screening in first trimester (PAPP-A)
- Early DM screen
- Thrombophilia workup
- Second trimester maternal serum screening (MSAFP)
- Fetal anatomic survey

Management of subsequent pregnancy: Third trimester

- Maternal assessment of fetal movement:
  - 28 weeks
- Serial sonograms for fetal growth (every 4 weeks, starting at 28 weeks)
- Doppler studies - IUGR
- Twice weekly NSTs/AFI (BPP) initiated at 32 weeks or 1-2 weeks before GA of previous stillbirth

Heinonen, Birth, 2000
Management of subsequent pregnancy: Delivery plan

- Timing delivery depends in maternal anxiety, cervical ripeness, and cause of previous loss
  - Elective induction at 39 weeks gestation or with pulmonary maturity (if earlier delivery desired)

The largest category of conditions associated with stillbirth is:
- a. Inheritable genetic syndromes
- b. Fetal growth restriction
- c. Epigenetic syndromes
- d. Maternal thrombophilias
- e. Diabetes

A woman has a stillborn infant at 36 weeks of gestation during her first pregnancy. The most likely outcome for her next pregnancy is:
- a. Recurrent stillbirth
- b. Intrauterine growth restriction
- c. Cesarean delivery
- d. Preterm delivery
- e. Normal term delivery
A woman has a stillborn infant at 36 weeks of gestation during her first pregnancy. During her second pregnancy she undergoes a first trimester test of her pregnancy-associated plasma protein A (PAPP-A) that is reported to be below the 5th percentile. This patient’s risk of a stillbirth due to placental dysfunction during this pregnancy is approximately:

a. 2%
b. 22%
c. 42%
d. 62%
e. 82%

In the absence of a fetal neural tube or ventral wall defect, the finding of elevated maternal serum alpha fetoprotein (MSAFP) is thought to reflect:

a. Fetal growth restriction
b. Abnormal placentation
c. Maternal liver dysfunction
d. Fetal liver dysfunction
e. Fetal renal dysfunction

Which of the following characterizes the changes that uterine spiral arteries undergo to support normal placentation?

a. High resistance, high compliance
b. High resistance, low compliance
c. Low resistance, high compliance
d. Low resistance, low compliance
When evaluating a growth restricted fetus, which of the following will indicate declining fetal status first?

a. Umbilical Doppler studies  
b. Middle cerebral artery Doppler studies  
c. Fetal nonstress test  
d. Contraction stress test  
e. Biophysical profile

In otherwise healthy women with a history of a prior stillbirth, antenatal testing should be begun at approximately:

a. 26-28 weeks  
b. 29-31 weeks  
c. 32-34 weeks  
d. 35-37 weeks  
e. 38-40 weeks

Stillbirth Collaborative Research Network (SCRN)

- Multi-center NICHD sponsored trial
- RFA in response to 2001 workshop
  - Setting a research agenda for stillbirth
    - Under-reporting of stillbirth
    - Poor quality death certificates
    - No standard “work-up”
    - Low autopsy rates
    - Few population-based studies
Clinical Sites: 59 hospitals

Independent datacenter & NICHD

- University of Utah
- Brown University
- Emory University
- RTI International
- University of Texas Medical Branch, Galveston
- University of Texas, San Antonio
- NICHD
- Brown University

Study Design: Cohort and nested case control studies

- Cohort
  - Geographic population-based
  - 59 hospitals - 90% ascertainment
  - Incidence of stillbirth
  - Comparison to vital statistics departments

SCRN Study Design

- Nested case control studies
  - Risk factors and etiologies of SB
    - Stillbirths identified at time of delivery
    - Live births identified via random selection at time of delivery
  - over-sampling of live births of African descent and < 32 wks
**SCRN Study Design**

- Standardized protocol:
  - Maternal interview
  - Medical record abstraction
  - Postmortem (SB only) and placental pathology
  - Bio-specimen collection
  - Testing to assess causes / risk factors
  - Central data collection and analysis

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**Sample Size**

- 700 SB (500 with complete postmortem)
- 1903 LB
  - 1377 randomly sampled > 32 weeks
  - 198 randomly over-sampled < 32 weeks
  - 328 from eligible births 20 – 23 weeks
- Approximately 3 year accrual period
- Greater than 1:1 ratio of LB to SB across ethnic categories and gestational age

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**SCRN Overarching Hypotheses**

1. Use of a prospectively implemented, standardized, postmortem and placental examination protocols will improve diagnosis of fetal or placental conditions that cause or contribute to stillbirth
2. Use of standardized surveillance in a geographic area will show that the stillbirth rates are greater than those reported to vital statistics.

3. Maternal biologic and environmental risk factors in combination with genetic predisposition increase the risk for stillbirth.

Detailed hypotheses that span these 3 overarching hypotheses:

- Five areas:
  - Postmortem and placental examination
  - Surveillance and epidemiology
  - Genetics
  - Maternal disease mechanisms
  - Immunology / Infectious disease
Case 1

- 27 year old woman with uncomplicated prenatal course
- 24 weeks diagnosed with fetal death in office
- MFM performs ultrasound
Most likely cause?

- Down syndrome
- Trisomy 18
- Trisomy 13
- Turner syndrome (XO)

Subsequent pregnancy

- Patient returns 4 months later for MFM consult and is 8 weeks pregnant
- Counseling regarding recurrence risk
- Plan of management for this pregnancy
How would you counsel this patient?

- Increased risk of aneuploidy
- No increased risk of aneuploidy
- Unknown

Nuchal translucency

“Patients who have had a previous fetus or infant with Turner syndrome may be offered chromosome analysis in a subsequent pregnancy for reassurance.”
Case 2

- 34 year old G1P0 with uncomplicated prenatal course diagnosed with 35 week stillbirth
- Birth weight= 1470 grams
- Declined autopsy: no gross morphological abnormalities
- Placental pathology performed
- No personal or family hx of thrombosis
- Thrombophilia workup sent 6 weeks postpartum

Placental Pathology:

- Patient returns 4 months later for MFM consult for preconception care
- Counseling regarding recurrence risk of stillbirth
- Plan of management for this pregnancy
How would you manage this patient?

- No treatment
- Baby ASA
- Heparin
- Baby ASA/Heparin