How to Assess Stillbirths and Miscarriages

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Objectives for management of miscarriage or stillborn

- Closure for the family
- Identify the conditions that have been best demonstrated to cause miscarriage or stillbirth
- Evaluate both adverse events using the most effective workup
- Accurately formulate an etiology for the event when possible
- Confer with experts to employ the best recommended hospital policies for management of stillbirth

Definitions

Spontaneous abortion
- Miscarriage
- <20 weeks gestation or <500g

Intrauterine fetal demise
- “Stillbirth”
- >20 weeks gestation or >350g—state dependent
- >500g is 50%ile for 20 weeks gestation
- Illinois: >20 weeks gestation
- “Delivery of a fetus showing no signs of life as indicated by the absence of breathing, heart beats, pulsation of the umbilical cord, or definite movements of voluntary muscles”
- Does not include terminations of pregnancy or IOL for previable PPROM

Causes of stillbirth

- >30 classification systems exist
- Important to distinguish between
  - Underlying cause of death
  - Mechanism of death
  - Risk factors

The National Institute of Child Health and Human Development
Classification of stillbirth

Classification of Stillbirth

- Eunice Kennedy Shriver workshop 2007
- National Institute of Child Health and Human Development
- "An optimal classification system would identify the pathophysiologic entity initiating the chain of events that irreversibly lead to death"

Criteria for “cause”

- Epidemiologic data demonstrate an excess of stillbirth associated with that condition
- Biologic plausibility that the condition causes stillbirth
- Either rarely seen in association with live births or, when seen in live births, results in a significant increase in neonatal death
- A dose-response relationship exists
  - The greater the “dose” of the condition, the greater the risk of fetal death
- Associated with evidence of fetal compromise
  - The stillbirth likely would not have occurred if that condition had not been present
Causes of stillbirth

- Severe maternal illness
- Placental infection that prevents oxygen/nutrients from crossing to the fetus
- Fetal infection that causes a lethal congenital deformity

Infections

- Associated with 10-20% of stillbirths in developed countries
- Higher association with preterm birth
- Sometimes difficult to prove causality

Mechanism of fetal death

- Severe maternal illness
- Placental infection that prevents oxygen/nutrients from crossing to the fetus
- Fetal infection that causes a lethal congenital deformity
- Fetal infection that damages a vital organ
- Precipitation of preterm labor, with intrapartum fetal death

Infections Should Be Proven

- Signs of infection in the fetus
- Evidence on autopsy of extensive organ involvement
- Positive fetal cultures
- Positive maternal cultures plus chorioamnionitis/funisitis

Causes of IUFD: Spirochetes

<table>
<thead>
<tr>
<th>Organism</th>
<th>Maternal Disease</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Treponema pallidum}</td>
<td>Syphilis</td>
<td>Rare</td>
</tr>
<tr>
<td>\textit{Borrelia burgdorferi}</td>
<td>Lyme disease</td>
<td>Typhus</td>
</tr>
<tr>
<td>\textit{Borrelia recurrentis}</td>
<td>Relapsing fever</td>
<td>Tick borne, endemic in the Western US, rare cause of stillbirth</td>
</tr>
<tr>
<td>\textit{Borrelia duttonii}</td>
<td>Relapsing fever</td>
<td>Tick borne, sub-Saharan Africa, important cause of stillbirth</td>
</tr>
<tr>
<td>\textit{Leptospira interrogans}</td>
<td>Leptospirosis</td>
<td>Uncommon</td>
</tr>
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Protozoa

<table>
<thead>
<tr>
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<tr>
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<td>\textit{Chagas disease}</td>
<td>Kissing bug</td>
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<tr>
<td>\textit{Plasmodium falciparum}</td>
<td>Malaria</td>
<td>Common in endemic areas</td>
</tr>
<tr>
<td>\textit{Plasmodium vivax}</td>
<td>Malaria</td>
<td>Malaria</td>
</tr>
<tr>
<td>\textit{Toxoplasma gondii}</td>
<td>\textit{Toxoplasmosis}</td>
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Protozoa: Severe placental dysfunction

Causes of IUFD: Protozoa

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Protozoa: Severe placental dysfunction

Causes of IUFD: Protozoa

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Protozoa: Severe placental dysfunction
Viruses

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<tr>
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</thead>
<tbody>
<tr>
<td>Parvovirus B19</td>
<td>Erythema infectiosum</td>
<td>Likely the most common viral etiologic agent</td>
</tr>
<tr>
<td>Coxsackie A and B</td>
<td>Various</td>
<td>May be important</td>
</tr>
<tr>
<td>Echovirus</td>
<td>Various</td>
<td>Importance unknown</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Various</td>
<td>Importance unknown</td>
</tr>
<tr>
<td>Hepatitis E virus</td>
<td>Fulminant hepatic failure</td>
<td>Especially in endemic areas</td>
</tr>
<tr>
<td>Rubella</td>
<td>Poly</td>
<td>Historic cause</td>
</tr>
<tr>
<td>Varicella</td>
<td>Chickenpox</td>
<td>Rare cause</td>
</tr>
<tr>
<td>Rubella</td>
<td>German measles</td>
<td>Rare in developed countries</td>
</tr>
<tr>
<td>Human</td>
<td>Parvovirus</td>
<td>Rare in developed countries</td>
</tr>
<tr>
<td>Rubella</td>
<td>Measles</td>
<td>Rare in developed countries</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Asymptomatic</td>
<td>Case reports</td>
</tr>
<tr>
<td>HIV</td>
<td>AIDS</td>
<td>Rare maternal disease</td>
</tr>
<tr>
<td>Influenza</td>
<td>Respiratory tract infection</td>
<td>Severe maternal disease</td>
</tr>
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</table>

Bacteria

<table>
<thead>
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<th>Maternal disease</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. Coli</td>
<td>Asymptomatic</td>
<td>Probably the most common organism associated with stillbirth</td>
</tr>
<tr>
<td>GBS</td>
<td>Asymptomatic</td>
<td>Common cause of stillbirth</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>Asymptomatic</td>
<td>Common cause of stillbirth</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>Asymptomatic</td>
<td>Common cause of stillbirth</td>
</tr>
<tr>
<td>Ureaplasma, mycoplasma</td>
<td>Asymptomatic</td>
<td>Common cause of stillbirth</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Listeriosis</td>
<td>Common cause of stillbirth</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Pelvic infection</td>
<td>Suggested cause—case reports</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Pelvic infection</td>
<td>Suggested cause—case reports</td>
</tr>
<tr>
<td>Candida albi</td>
<td>Thrush, vaginitis</td>
<td>Confirmed in case reports</td>
</tr>
</tbody>
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Maternal medical conditions

Causes of stillbirth—NICHHD workshop consensus

Hypertensive disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated stillbirth rate per 1000 births in patients with the condition</th>
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</thead>
<tbody>
<tr>
<td>All pregnancies</td>
<td>6-7</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>5-25</td>
</tr>
<tr>
<td>Superimposed preeclampsia</td>
<td>52</td>
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<tr>
<td>Gestational hypertension and mild preeclampsia</td>
<td>9</td>
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<tr>
<td>Severe preeclampsia</td>
<td>25</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>18-48</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>51</td>
</tr>
</tbody>
</table>

Diabetes

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<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>All pregnancies</td>
<td>6-7</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>5-10</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>0-10</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>25</td>
</tr>
</tbody>
</table>


Diabetes

Mechanism of fetal demise:
• Congenital abnormality
• Placental dysfunction
• Obstructed labor and intrapartum death
• Macrosomia
• Fetal hyperglycemia → fetal insulin production → excessive fetal growth → metabolic acidosis

To consider cause of death:
• Signs of intrapartum or intrapartum asphyxia
• LGA fetus
• SGA fetus
• Severe malformation
• Placenta demonstrates characteristic histologic findings
• Large edematous villi
• Increased prominence of cytotrophoblasts

Thyroid/renal disorders

Thyroid disorders
• Graves disease, where thyroid-stimulating hormone receptor antibody causes fetal toxicosis
• Untreated thyroid disorders

Renal disorders
• Linear relationship between maternal creatinine and risk of fetal demise

Systemic Lupus Erythematosus
• Stillbirth rates are higher in the presence of HTN, nephritis, or APL
• Circulating auto-antibodies, anti-Ro, anti-La
• Congenital heart block, hydrops

Maternal medical conditions

• Risk is a continuum

Thrombophilias

Antiphospholipid syndrome
• Inflammation, thrombosis, and infarction in the placenta
• Clear histopathological or clinical evidence of placental insufficiency

Thrombophilias should only be considered as the cause of stillbirth with:
• Evidence of placental insufficiency such as fetal growth restriction or infarction and
• Recurrent fetal loss

Alloimmunization Causes of stillbirth—NIHCHD workshop consensus

Red cell alloimmunization
• Anti-Rhesus D, anti-Rhesus C, anti-Kell
• Must have a positive indirect Coombs test
• Antibody titer more than 1:16 (or 1:8 for anti-Kell)
• Evidence of fetal anemia with hydrops
• Evidence of fetal extramedullary hematopoeisis

Platelet alloimmunization
• HPA-1a, HPA-5a, HPA-4
• Maternal antibodies against paternal and fetal platelet antigens
• Parental platelet incompatibility for the pertinent antigen
• Fetal thrombocytopenia
• Massive intracranial hemorrhage
Congenital malformations
Chromosomal abnormalities

Causes of stillbirth—NIHCD workshop consensus

Criteria
- Epidemiologic data demonstrating an excess of intrauterine mortality
- Seen rarely in liveborn neonates
- When seen in liveborn neonates, it frequently results in neonatal death
- Biologic plausibility that it can result in death

Congenital malformations
Chromosomal abnormalities

Incidence
- Cytogenetic abnormalities account for 6-13% of all stillbirths
- This may be higher because 40-50% attempted karyotypes fail to grow
- 23% monosomy X, 23% trisomy 21, 21% trisomy 18, 8% trisomy 13

Fetomaternal hemorrhage
Causes of stillbirth—NIHCD workshop consensus

- The cause 4% of all stillbirths
- Risk factors:
  - Placental abruption
  - Abdominal trauma
  - Multiple gestation
  - Abnormal fetal testing

Fetomaternal hemorrhage

- Risk of stillbirth depends on
  - Amount of hemorrhage
  - Acute/chronic
  - Gestational age
  - A threshold of 20 mL/kg of fetal bleeding is associated with increased risk of stillbirth
  - Autopsy confirmation of fetal anemia and hypoxia
Placental causes
Causes of stillbirth—NIHCHD workshop consensus

- Placenta previa, vasa previa, neoplasms
- Placental abruption has 8.9 relative risk of stillbirth
  - May be considered the cause of death if >30% of the placenta shows signs of abruption


Placental causes

- Any disease that causes an SGA placenta may result in stillbirth
  - <5% expected weight for gestational age
  - Preeclampsia, DM, HTN, renal, chronic infections
- Any disease that causes an LGA placenta may result in stillbirth
  - >95% expected weight for gestational age
  - Hydrops fetalis, DM, syphilis

Umbilical cord pathology
Causes of stillbirth—NIHCHD workshop consensus

- Account for 3.4-15% of stillbirths
- Velamentous insertion
  - If it leads to a vasa previa or bleeding during labor
- Umbilical cord prolapse
  - Associated with prematurity, malpresentation, multiparity, obstetric manipulation
- Umbilical cord occlusion
  - Cord prolapse, entanglement (mono-mono twins)
  - Torsion
  - Rupture, strictures, hematomas

Umbilical cord pathology

- Nuchal cord
  - Occur
  - Not associated with an increased risk of stillbirth in study of 14,000 deliveries
- True knot
  - Also common in live births
  - Grooving of the cord, constriction of the umbilical vessels, edema, congestion, thrombosis
  - Required to claim it is the etiology
  - Isolated finding of a nuchal cord or a true knot at the time of delivery is insufficient evidence that cord accident is the cause of stillbirth
  - Exclude other relevant causes of stillbirth
  - Find evidence of hypoxia and cord occlusion on postmortem examination

Complications of multifetal gestation

- Monochorionic placentation
  - Twin-twin transfusion syndrome occurs in 9% of mono- mono twins
  - Mortality can be 90% in untreated cases

Complications of multifetal gestation

- Mono- mono twins
  - Cord entanglement, preterm birth, growth impairment, malformations, genetic abnormalities, vascular anastomoses

Uterine complications

• Uterine rupture
  • Evidence of obstructed circulation
• Uterine abnormalities
  • There is an increased risk of uterine abnormalities in women with recurrent pregnancy loss/stillbirth
  • Possibly due to poorly vascularized uterine tissue or space constraints
  • Increased risk of PPROM, cervical insufficiency, preterm labor
  • Septate uterus has highest risk of stillbirth and placental abruption

• Evidence of obstructed circulation

Importance of a stillbirth evaluation

• Counseling for risk of recurrence
• Possible intervention to reduce recurrence risk
• Facilitate emotional closure and healing

Most stillbirths remain unexplained

• Incomplete evaluation
  • Lack of clinician awareness
  • Concerns of the family
  • Lack of single universally accepted classification scheme
  • Difficult to assign a definitive cause
• Unknown cause
  • Sometimes despite thorough evaluation

Overview

<table>
<thead>
<tr>
<th>Recommended studies</th>
<th>Sometimes helpful</th>
<th>Not generally useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autopsy</td>
<td></td>
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<tr>
<td>Placental pathology</td>
<td></td>
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<tr>
<td>Karyotype</td>
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<tr>
<td>Chromosomal microarray</td>
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<tr>
<td>Kliehauer–Betke</td>
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<tr>
<td>Indirect Coombs</td>
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<tr>
<td>Acquired thrombophilia panel</td>
<td></td>
<td></td>
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<tr>
<td>Anti-B2-glycoprotein</td>
<td></td>
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<tr>
<td>Toxicology screen</td>
<td></td>
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<tr>
<td>Syphilis serology</td>
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<td>Glucose screening</td>
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<td>TSH</td>
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<td>CMV, toxoplasmosis, other infectious</td>
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<td>Bile acids</td>
<td></td>
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<tr>
<td>Sonohysterogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine TORCH titers</td>
<td></td>
<td></td>
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<tr>
<td>ANA testing</td>
<td></td>
<td></td>
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<tr>
<td>Cultures of placental membranes</td>
<td></td>
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Time of demise

<table>
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<tr>
<td>Brown or red discoloration of the cord stump</td>
<td>6 hours ago</td>
</tr>
<tr>
<td>Desquamation of face, back, abdomen</td>
<td>12 hours ago</td>
</tr>
<tr>
<td>Desquamation &gt;1/2 of the body or &gt;2 body zones</td>
<td>24 hours ago</td>
</tr>
<tr>
<td>Skin color brown or tan</td>
<td>36 hours ago</td>
</tr>
<tr>
<td>Mummification: (reduced soft tissue, leathery skin, dark brown)</td>
<td>52 hours ago</td>
</tr>
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Kumar: Robbins pathologic basis of disease, 8th edition, 2009
Autopsy

- New information that influences counseling in 26-51% of cases
- Valuable However, it is performed in <50% of cases
  - Clinician hesitation to recommend autopsy
  - Patient reservations

Alternatives to autopsy

- MRI
- Radiographs for skeletal dysplasias
- Partial autopsy
  - Head sparing autopsy (may miss CNS pathology)
- External examination by a trained pathologist
  - Can identify syndromes, congenital anomalies, timing of death, growth anomalies
  - Will likely miss fetal infections and internal anomalies
- External examination with selected biopsies
  - More likely to identify fetal infection

Alternatives to autopsy: MRI

**Advantages**
- Very good for CNS pathology
- Sometimes better than autopsy, because fetal brain has high water content and liquefies
- Fluid collections and effusions in the body

**Disadvantages**
- May miss cardiac anomalies, bowel anomalies
- Cannot diagnose infections or metabolic disease

Examination of the placenta

- The most valuable diagnostic test in most studies
  - Dutch study showed it to be valuable in 95% of cases
  - Provides additional information in 30% of cases

Examined of the placenta

- Weight in relation to norms for gestational age
- Evidence of abruption, infarction, thrombophilias
- Hemosiderin deposits = chronic abruption
  - Perivillous and marginal fibrin deposition
  - Decidual necrosis
  - Evidence of infarction

- Multiples: chorionicity, vascular anastomoses in multifetal gestations
- Cord: thrombosis, velamentous cord insertion, vasa previa
- Evidence of infections
  - More common in preterm stillbirth
  - Viral nucleic acid amplification
  - Bacterial cultures
Karyotype/Chromosomal microarray

• Abnormal fetal karyotype noted in 8-13% of all stillbirths and in >20% of those with morphologic abnormalities or IUGR
• Dutch study: 11.9% prevalence of a chromosomal abnormality in the 362 IUFDs who underwent karyotyping
  • 37% trisomy 21, 16% monosomy X, 4% trisomy 13
• Karyotype was valuable in 29% of cases
• FISH can also be performed

If live cells are not available: Microarray

• Screens the genome for copy number variations (CNPs)
  • BAC arrays provide overview of genome
  • SNP arrays provide more detailed coverage with probes on every 100-1000 base pairs
  • Detects deletions, duplications, aneuploidies, unbalanced translocations with a gain/loss of sequences
  • Good for small deletions or cryptic changes
  • Cytogenetics resolution is only 5-10Mb

Microarray versus karyotyping

• Reddy U.M et al, 2012: Prospective population-based study of 532 stillbirths over 2 years
• Patients with IUFD underwent:
  • Interview, chart abstraction, postpartum examination, placental pathology, karyotype analysis, and specimen collection
  • DNA analyzed with an SNP microarray with data aligned to Human Genome release 18

Microarray versus karyotyping

• Microarray analysis yielded a result in 87.4% stillbirths compared to 70.5% for karyotype
• 85.2% of these were benign, too small, or probably benign
• 2.6% were pathogenic, 6.9% were aneuploid
• Microarray detected CNV consistent with DiGeorge syndrome not detected by karyotype in 3 cases

Maternal Workup

Laboratories (Recommended)

• CBC
• Kliehauer-Betke
• Human parvovirus B-19 IgG and IgM
• Lupus anticoagulant, anticardiolipin antibodies
• Indirect Coombs
  • If not already done antepartum
• Toxicology screen

Kliehauer Betke

• Recommended to do before induction of labor
• However, given that only massive hemorrhage is likely to cause fetal death, can also be done up to 2-3 weeks after delivery
• In one study, FMH was a contributing factor in 10.6% of the total cohort
Antiphospholipid antibodies

- One fetal death satisfies criteria for testing
- Confirm with repeat testing in 6–12 weeks
- More likely positive if stillbirth was accompanied by IUGR or severe preeclampsia
- Two Dutch studies (750 fetal deaths in Korteweg et al. 2010, 1025 fetal deaths in Korteweg et al. 2012) showed that neither testing for acquired nor inherited thrombophilia is valuable
- Unless the patient has a family or personal history of thrombophilia

Laboratories (Sometimes useful)

- Syphilis
- TSH
- Inherited thrombophilia workup
  - Factor V Leiden, prothrombin gene mutation, antithrombin III, fasting homocysteine
- Glucose screening
- Sonohysterogram
  - Especially if loss associated with preterm labor, PPROM, cervical insufficiency, previable gestations, fetal malpresentation

Guided by maternal history and risk factors

Inherited thrombophilia

- Korteweg et al. 2010. Multicenter, prospective study. 750 singleton fetal deaths >=20 wks, excluding terminations
- Tested for vWF, antithrombin, protein C, total and free protein S, prothrombin gene mutation, factor V Leiden
- Cause of death classified by a panel
- “Except for vWF and paternal free protein S, acquired and thrombophilic defects were not more prevalent after fetal death.”
- However, many case-control studies show an association

Laboratories (unproven benefit)

- Toxoplasmosis, rubella, CMV, HSV, other infections
  - Viruses for which vaccines are prevalent are uncommon in developed countries
- However, if autopsy, pathology, or history is suggestive, take maternal/neonatal serology, special tissue stains, testing for nucleic acids
- ANA

Considerations

- Parents benefit from seeing/holding the infant
  - Warn them about how the baby will appear
- Use the term “baby”
- Encourage parents to name the infant
  - Knowing the sex is important
- Fetal loss can be devastation at any gestational age
- Different cultures grieve in different ways
Conclusions

• The cause of a stillbirth is the initial pathophysiologic entity that irreversibly led to fetal death
• Cause must be proven with evidence of fetal harm
• There are many benefits to finding a cause
• Encourage patients to allow an evaluation within the boundaries of their personal and cultural values

Conclusions

• Recommended laboratories are CBC, Kliehauer-Betke, parvovirus B-19 IgG and IgM, lupus anticoagulant, anticardiolipin antibodies, and toxicology screen
• Only perform other labs as indicated by maternal history
• Encourage patients to receive an autopsy
• Partial autopsy and MRI are alternatives
• Always send the placenta to pathology

Causes of miscarriage

• PUBMED search – “causes of miscarriage,” 24,817 articles from 1873 to 2017
• Original reference “On the causes of Unavoidable Haemorrhage during Miscarriage or Labour when the Placenta is Previa,” Duncan, JM. British Medical Journal 22;2(673):597-599, 1873

Causes of Miscarriage

• ANEUPLIOIDY
• Historic data suggests that 50% of first trimester miscarriages are due to aneuploidy
• Recent data is confirmatory (Qu et al., 2017)
  • 468 products of conception were evaluated by single nucleotide polymorphism (SNP array) or karyotype analysis
  • Mean gestational age at miscarriage 9.4 weeks (4 to 13 weeks)
  • Mean age of pregnant women was 19-47 years old

Causes of Miscarriages (Qu et al., 2017)

<table>
<thead>
<tr>
<th>Frequency of Anomaly (%)</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosomy</td>
<td>1</td>
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<tr>
<td>Trisomy</td>
<td>1</td>
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<tr>
<td>Isolated sex</td>
<td>2</td>
</tr>
<tr>
<td>Balanced translocation</td>
<td>3</td>
</tr>
<tr>
<td>Balanced rearrangement</td>
<td>4</td>
</tr>
<tr>
<td>Balanced translocation</td>
<td>5</td>
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<tr>
<td>Balanced translocation</td>
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<td>Balanced translocation</td>
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<td>Balanced translocation</td>
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<td>Balanced translocation</td>
<td>9</td>
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<td>Balanced translocation</td>
<td>11</td>
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<tr>
<td>Balanced translocation</td>
<td>12</td>
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<td>Balanced translocation</td>
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</tr>
<tr>
<td>Balanced translocation</td>
<td>X</td>
</tr>
</tbody>
</table>
Causes of Miscarriages (Qu et al., 2017)

Maternal Age

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-20</td>
<td>25.0%</td>
</tr>
<tr>
<td>21-24</td>
<td>30.0%</td>
</tr>
<tr>
<td>25-29</td>
<td>45.0%</td>
</tr>
</tbody>
</table>

Chromosomal Anomaly/Gestational Age

<table>
<thead>
<tr>
<th>Gestational Age (weeks)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-9</td>
<td>59.7%</td>
</tr>
<tr>
<td>9-12</td>
<td>59.0%</td>
</tr>
<tr>
<td>12-15</td>
<td>64.0%</td>
</tr>
</tbody>
</table>

Uniparental Isodisomy

- Endometriosis – increases risk, particularly mild endometriosis associated with pro-inflammatory state (adjusted risk 1.97 (CI 1.41-2.75))
- Low dose aspirin and recurrent pregnancy loss
- Schaidman et al., 2014 – Low dose aspirin does not appear to be an effective treatment for patients with prior pregnancy losses
- IVS in recurrent pregnancy loss
- Christiansen et al., 2014 – in a small study IVS does not appear to be effective for women with secondary recurrent pregnancy loss
- Obesity and weight gain before pregnancy
- Gaylin et al., 2014: in data from the Nurses' Health Study showed that obesity and weight gain before pregnancy is associated with pregnancy loss
- IVF for recurrent pregnancy loss
- Murugappan et al., 2016: expectant management in unexplained recurrent pregnancy loss is as successful as IVF preimplantation genetic testing and had a lower median time to pregnancy
- Chronic endometriosis
- Bouak et al., 2016: Chronic endometritis is associated with recurrent pregnancy loss. Office hysteroscopy could aid in diagnosis by immunohistochemistry for syndecan 1.

Miscarriage and treatments

- Fligner CL, Dighe M. “Fetal and Perinatal Death Investigation: Redefining the Autopsy and the Role of Radiologic Imaging.” Ultrasound Clin 8, 2012 (S2-S17)
- Illinois Masonic Medical Center Perinatal Loss Policy: Policy 10.116.044