Post-mortem evaluation of a stillborn: a conversation between the pathologist and the obstetrician/midwife

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Beyond just the “why”
- The family
  - Cause of death
  - Risk of recurrence
- The OB/CNM
  - Additional learning points for best practices
- Public health issues
  - Strategies for prevention
  - Allocation of resources

What tests to order
- Autopsy
- Placental exam
- Maternal tests
Maternal tests (recommended in all stillbirths)
- Complete blood count
- Kleihauer-Betke test (for fetomaternal hemorrhage)
- Fasting glucose, glycated hemoglobin
- Blood antibody screen (red cell alloimmunization)
- Thyroid function tests
- TORCH titers

Maternal tests (if indicated)
- Urine toxicology
- Autoimmune work-up (Lupus anticoagulant, anticardiolipin antibody titers, etc)
- Thrombophilia work-up

Placental exam
- Should ALWAYS be examined, even in the absence of autopsy
- Sampling
  - Umbilical cord (2)
  - Membrane roll
  - Placental disc (5 normal + all lesions)
- Cultures and cytogenetics can also be done from the placenta
Autopsy

- Full autopsy (without restrictions) plus placental exam are the most optimal for cause of death determination
- Routine tests during autopsy
  - Gross examination with photography
  - Radiography*
  - Bacterial cultures
  - Cytogenetics*
  - Histology

What to provide the pathologist

- A completed consent form
  - Limited vs. detailed exam (patient’s wishes)
    - Other limitations (excluding brain examination; return organs to the body; examination of specific organs only; etc.)
  - **KNOWING THE BASICS HELPS WITH PARENTAL COUNSELING REGARDING CONSENT**
  - Does the patient have any specific questions/concerns?
  - What is YOUR question as OB/CNM?

What to provide the pathologist

- Thorough maternal history
  - Pre-pregnancy disease
  - Prenatal course
  - Smoking, etc.
- Thorough delivery note
  - Note any unusual findings (i.e. focal cord thinning)
  - Note full length of the umbilical cord
  - In cases of nuchal cord, indicate tight vs. loose
**Autolysis**

- Demise-to-delivery period
  - Often unknown at the time of diagnosis
- Post-delivery period
  - Limit to 48 hours where possible
  - Limit these as much as possible, while respecting the patient’s wishes

**Autopsy: requesting clinician’s responsibilities**

- Be present, at least for the external exam
- Know the basics
  - Often, the pathologist will not be a trained pediatric/perinatal pathologist, but will be able to do additional testing or dissection if prompted

**Autopsy: pathologist’s responsibilities**

- Review the complete medical records
  - Maternal medical history
  - Obstetric history (past and present)
- Communicate with the requesting clinician
  - Specific questions
Autopsy: gross examination

- Weight at autopsy
  - compare to birthweight
- Foot length, crown-rump length (for confirmation/determination of GA)
  - Compare to clinically-determined gestational age (first trimester ultrasound is best)
  - If anatomic dating is 2 or more weeks behind clinical dating: consider symmetric growth restriction

Fetal growth

- Birthweight
  - Vs. weight at autopsy (usually lower)
- Brain: liver weight ratio
  - Normal is 3:1 (seen in both normal growth and symmetric growth restriction)
  - >3:1 indicates asymmetric fetal growth restriction
  - <3:1 often correlates with macrosomia

Autopsy: gross examination

- Malformations/syndromes
  - Dysmorphic facial features
  - Neural tube defects
  - Short long bones
- Document
  - Gross photographs (more is better)
  - Radiographs
**Autopsy: “routine” tests**
- Bacterial cultures
  - Blood
  - Lung/spleen tissue
- Cytogenetics*
  - Low yield if there is no evidence of dysmorphic features/structural abnormalities/hydrops
    (*ACOG recommendations: Microarray)
- In-situ exam and weight of all organs
- Histology

**Autopsy: Histology**
- Determination of timing of demise (with respective to delivery)
- Leave stomach intact
  - Evaluate contents (neutrophils)
- Suspicion of structural cardiac defects
  - Fix heart/lung block for later dissection
- Tissue can be frozen for additional testing (i.e. for metabolic diseases)

**Approach to a perinatal autopsy**
- The anomalous fetus
- The premature liveborn fetus
- The stillborn fetus
  - Fresh vs. macerated
- Multiple gestation
- Hydrops fetalis
The anomalous fetus

- Antenatal diagnosis (ultrasound)
- Careful documentation of gross findings
  - Gross photographs (consult a pediatric dysmorphologist)
  - Radiography if indicated
  - Careful dissection of the heart
- Ruling out artifact
- Placenta is usually non-contributory
  - **except to rule out amnion band sequence**

Example of artifact

- Asymmetric vs. symmetric findings
  - When asymmetric, consider artifact

Amniotic band sequence

- Strips of thin membrane in and around asymmetric anomalies
  - i.e. amputation of random digits
- Evaluate the placenta
  - will show amnion detachment/degeneration
- Generally considered non-recurrent (vs. some genetic malformations)
Amniotic band sequence

"STRING" TETHERED TO MISSING FINGER

The premature liveborn fetus-1
- Non-anomalous fetus, 28-36 weeks GA
- Evaluation of lungs
  - Maturity (histology)
  - Evidence of respiratory failure (histology)
- Evaluation of amniotic fluid infection
  - Placental examination (chorioamnionitis with a fetal response)
  - Stomach contents (neutrophils)
  - Lung: cultures and histology ("congenital pneumonia")

Amniotic fluid infection
Amniotic fluid infection

Example of a case with "fetal response"

The premature liveborn fetus-2
- Non-anomalous fetus, 20-28 weeks
- Evidence of amniotic fluid infection and "abruption" ("Inflammatory abruption")
- Placental examination is key
  - Chorioamnionitis, +/- fetal response
  - Marginal/retroplacental hematoma
- Pathologic correlate of maternal cervical incompetence
  - Does not correlate with placental insufficiency

Inflammatory abruption sequence
- 22-week GA
- Normal weight
- Marginal hematoma
The stillborn fetus - 1
- Obstetric trauma
  - Thankfully rare
  - Consultation with medical examiner

The stillborn fetus - 2
- Maternal disease
  - Diabetes
    - Fetal macrosomia
      - Islet cell hyperplasia; cardiomegaly with myocardial hypertrophy; fetal malformation (esp. GU anomalies)
    - Placentomegaly
  - Hypertension
    - Fetal growth restriction (asymmetric)
      - Can also be symmetric if severe, +fetal malformations
    - Placental "Insufficiency": small placenta, hypermaturity, infarction, abruption

Placental insufficiency
Malformation in the setting of severe FGR
- 25 week GA with severe early-onset pre-eclampsia
- Severe symmetric and asymmetric fetal growth restriction
- Ambiguous genitalia

Blind vaginal pouch
- Bilateral undescended testes
  - Diagnosed as hypospadias secondary to severe fetal growth restriction
  - Karyotyping not required

The stillborn fetus-3
- Maternal sepsis/blood-borne infection
  - Including: CMV, HSV, parvovirus, streptococcal infections
  - History is not always supportive
  - Placental examination is key: chronic villitis
    - Viral inclusions
    - Immunohistochemistry
    - PCR-based assays

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History is not always supportive
Villitis

- Chronic villitis
  - TORCH (minority)
    - CMV (inclusions)
    - Syphilis (perivascular onion skining)
    - Toxoplasmosis (cysts in Wharton's jelly)
  - Unknown etiology (majority)

Example of infectious villitis (CMV)

The stillborn fetus-4

- Cord "accident"
- Clinical history is important
  - Nuchal cord, cord prolapse
- Acute anoxic event
  - Pathologist must exclude other causes of death
  - Document marks on the fetus
  - Placental pathology (gross & histology)
- Subacute-to-chronic (intermittent) hypoxia
  - Placental pathology (gross & histology)
Obstructive lesions of the umbilical cord

Long umbilical cord
- Term stillbirth
  - Deemed a "cord accident" by clinician; no autopsy was performed
  - Placental examination reveals an umbilical cord length of 117 cm (this is only noted in the gross description)
Long umbilical cord

- Obstetric history: prior term stillbirth with a cord length of 106 cm
- NOT a typical “cord accident”
  - “Cord accident” implies a non-recurrent lesion
  - Long umbilical cord is associated with a slightly higher risk of recurrence in subsequent pregnancies

Long, hyper-twisted umbilical cord:
51.7 cm; normal for this gestational age is 23-41 cm; with 13 twists/10 cm

Small placenta: 80 grams; <10th percentile for gestational age.

The stillborn fetus-5

- Recurrent fetal loss in the second trimester
  - Less likely due to cytogenetic abnormalities (compared to recurrent first trimester loss)
  - Cervical incompetence
  - Underlying endometritis?
  - Maternal autoimmune disease*
  - Villitis of unknown etiology (VUE)*
    - Rare variant: Massive chronic intervillositis
Maternal autoimmune disease

Villitis of unknown etiology
- Extensive villitis (multifocal)
- Rule out infectious etiology
- Recurrent in 10-15% of cases

Massive chronic intervillitis
- >50% recurrence rate
Multiple gestation
- Placental examination is key
- Monochorionic placentation
  - Twin-to-twin transfusion syndrome
- Monochorionic monoamniotic twins (in the same sac)
  - Umbilical cord obstruction

Twin-twin transfusion syndrome

Monochorionic monoamniotic twins
- High risk of cord entanglement
### Hydrops fetalis

- Most challenging in terms of etiology
- Cause of death
  - Liveborn: pulmonary hypoplasia
  - Stillborn: cardiac failure
- Differential diagnosis
  - Immune vs. non-immune-mediated

### Hydrops fetalis

- Karyotype (r/o aneuploidies)
- Bacterial and viral cultures (parvo, Listeria, CMV, Herpes, etc)
- Cardiac lesions
  - Premature closure of foramen ovale
  - Neoplasm (rhabdomyoma)
- Thoracic lesions
  - Congenital diaphragmatic hernia
  - Congenital cystic adenomatoid malformation

### Hydrops fetalis

- Fetomaternal hemorrhage
  - Kleihauer-Betke test
- GU malformations
  - Polycystic kidney disease
  - Cloacal malformation
- Metabolic diseases
  - Tissue frozen (for send-out tests) or fixed for electron microscopy
- Placental exam
  - Chorangioma
Chorangioma

High risk of complications (including hydrops) when tumor >5cm

Classification systems

- Conventional
  - Wigglesworth (pathophysiology)
  - Fetal & Neonatal classification
  - Revised obstetric (Aberdeen) classification
- Newer classification system: ReCoDe
  - Compared to Wigglesworth, reduced the percentage of “unexplained” stillbirth (from 57.7% to 15.2%)
  - Large portion (~43%) fall into category of “fetal growth restriction”

Gardosi et al. 2005

Positive vs. negative findings

- Negative findings are also important
  - Absence of villitis of unknown etiology, decidual vasculopathy (evidence of maternal vascular disease), and increased perivillous fibrin deposition (evidence of maternal autoimmune disease) reduces the recurrence risk
- Cord accident
  - Normally non-recurrent, except in case of an abnormally long UC (genetic component)
Discussion of autopsy findings with patient

- Prior discussion with pathologist
- Pathologist participation in the discussion with patient
  - With OB/CNM (in person)
  - After the initial meeting with OB/CNM (in person/by phone)

[Pathologists do not bill for autopsies, and cannot bill for appointments for such discussions]

Obtaining a perinatal pathology consult

- Perinatal records, autopsy findings, gross photos, and autopsy/placenta slides can be reviewed by a pediatric/perinatal pathologist
  - Sampling at the time of autopsy/placental examination is most important

References

- “Evaluation of Stillbirth” on UpToDate, by Dr. Drucilla Roberts
- “Approach to Perinatal Autopsy” Manual from Brigham and Women’s Women’s and Perinatal Pathology division
- AFIP Atlas of Placental Pathology