A practical and algorithmic approach to evaluation of the placenta
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Department of Pathology
UCSF

Speakers Disclosure
In the past 12 months, Drs. Kim, Cho, and Rabban have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in their presentations.

Outline
Surgical pathologist’s view point of placental pathology
• Inflammatory conditions
  – Grace E. Kim
• Vascular complications
  – Soo-Jin Cho
• Abnormal products of conception
  – Joe Rabban
• Questions

Inflammatory conditions of the placenta
• Gross review
• Select disorders
  – Those associated with adverse outcome, specifically long-term neurodisability
  – Definitions of terms
  – Specific etiologic examples

Conditions associated with adverse outcome
1. Acute chorioamnionitis with intense chorionic vasculitis
2. Prolonged chorionic plate meconium with associated fetal vascular necrosis
3. Villitis of unknown etiology with obliterative vasculopathy
4. Fetal thrombotic vasculopathy
• Pathologic umbilical cord lesions

Know basic clinical information
• Maternal history
  – Maternal preexisting disease
    • HTN, DM, thrombopathic conditions
  – Prior pregnancy history
• Neonate
  – Gestational age
  – Weight
  – Apgars
Maximize the histologic information obtained from each section
A1: Umbilical cord, fetal end unpainted and placental end painted
A2: Extraplacental membrane rolls, edge of disc to point of rupture
A3: Central, 2 cm from cord insertion, full thickness
A4: Peripheral, 2 cm from edge of disc, full thickness
A5+: Lesion(s)
Amnion
Wharton’s jelly
Smooth muscle wall of umbilical artery

Why is there a bite removed?
Where is all the extraplacental membrane?

Standard section (A2) rationale
Extraplacental membrane roll

• Thickest aspect, from point of rupture to include bite of placenta disc

Extraplacental membrane roll

All layers of extraplacental membrane

Extraplacental amnion membrane roll
Why is this a great section?

Standard sections (A3-A5+) rationale

- Full thickness section of disc
  To include chorionic plate vessels and adherent decidua
  - Central
  - Peripheral
  - Lesion/abnormalities

Maximize information obtained from a tissue section

<table>
<thead>
<tr>
<th>Amnion &gt;&gt;</th>
<th>Chorion + fetal vessels &gt;&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cottedons &gt;&gt;</td>
<td>Villi &gt;&gt;</td>
</tr>
<tr>
<td>Intervillous space &gt;&gt;</td>
<td></td>
</tr>
<tr>
<td>Decidua and maternal vessels &gt;&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meconium</td>
</tr>
<tr>
<td>Meconium</td>
</tr>
<tr>
<td>Fetal response to infection</td>
</tr>
<tr>
<td>Fetal vascular obstruction/chrombic vasculopathy</td>
</tr>
<tr>
<td>Both</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decidual vasculopathy</td>
</tr>
<tr>
<td>Chronic deciduitis</td>
</tr>
<tr>
<td>Retroplacental hematoma</td>
</tr>
</tbody>
</table>

Cassettes

A1: Umbilical cord, fetal end painted
A2: Extraplacental membrane rolls, edge of disc to point of rupture
A3: Central, 2 cm from cord insertion, full thickness
A4: Peripheral, 2 cm from edge of disc, full thickness
A5+: Lesion(s) %
What is your diagnosis?

**Final Pathologic Diagnosis:**
Acute chorioamnionitis

**Maternal inflammatory response**

- **Stage 1**
  - Early acute subchorionitis/chorionitis
    - Diffuse band of PMN below chorionic plate or at choriodecidual junction
- **Stage 2**
  - Acute chorioamnionitis
- **Stage 3**
  - Necrotizing chorioamnionitis
    - Neutrophil apoptosis and fragmentation
    - Amnion - thickened basement membrane and 30% of cells are desquamated
Acute chorioamnionitis
Extraplacental membrane

Fetal inflammatory response

• Stage 1
  – Umbilical phlebitis/chorionic vasculitis
• Stage 2
  – Umbilical arteritis
• Stage 3
  – Concentric periphlebitis/necrotizing funisitis

• High grade/severe
  – Intense chorionic vasculitis
• Prolonged
  – Necrotizing funisitis

Umbilical phlebitis + funisitis
Umbilical arteritis + funisitis

Inflammation? Yes, neutrophilic mainly

Acute chorioamnionitis
Extraplacemental membrane

Acute subchorionitis
**Chorionic vasculitis**

Downstream effects

Maternal neutrophils  Fetal neutrophils

Location: Yes, neutrophils are seen

Do you see the lesions?

Peripheral funisitis
Location: Yes, macrophages are seen.

Chlorohematoxylin, hematoxylin, hematoxylin.

Extensive chronic intervillositis

Meconium exposure, check for myonecrosis and villous alteration.

Hydropic villi
Immature villi

Hemosiderin

Chronic villitis, but typically lymphohistiocytic

Altered amniocytes & macrophages

Normal umbilical artery

Myonecrosis of umbilical cord artery

Pigmented macrophages in chorionic plate
Chorionic plate vessel myonecrosis and non-occlusive thrombus

Downstream effects

Chorionic plate vessel myonecrosis

Inflammation? Yes → Villi

Gram positive rod

Acute villitis and intervillus abscess

Intervillosus abscess
Acute chorioamnionitis

“Clouds” of bacteria

Gram positive rod

Acute villitis

Inflammation? Yes → Villitis

Chronic villitis

- Infectious
  - TORCH infections

- Villitis of unknown etiology (VUE)
  - Maternal immune response to an unknown antigen in fetal villous stroma
Distinction between VUE and infectious villitis

<table>
<thead>
<tr>
<th></th>
<th>VUE</th>
<th>Infectious villitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of pregnancy</td>
<td>Term/near term</td>
<td>Premature</td>
</tr>
<tr>
<td>Recurrence</td>
<td>10% - 15%</td>
<td>Rare</td>
</tr>
<tr>
<td>Signs &amp; symptoms of infection</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Extent of involvement</td>
<td>Terminal villi and stem villi only</td>
<td>Umbilical cord, chorionic plate, membrane - common</td>
</tr>
<tr>
<td>Pattern of involvement</td>
<td>Focal/patchy, others normal</td>
<td>Diffuse, varying severity</td>
</tr>
<tr>
<td>Duration of involvement</td>
<td>Recent; fibrin and necrosis</td>
<td>Long-standing; fibrosis/calcification</td>
</tr>
</tbody>
</table>

Infectious chronic villitis
90% due to syphilis and cytomegalovirus

- **Syphilis**
  - Placentomegaly, enlarged villi, necrotizing funisitis
  - Chronic villitis with prominent plasma cells
  - Spirochetes on silver stain

- **Cytomegalovirus**
  - Chronic lymphoplasmacytic villitis with viropathic inclusions
  - Multifocal small foci of villitis
  - Vasculitis of chorionic vessels may lead to thrombosis and hemosiderin deposition
Chronic lymphoplasmacytic villitis with hemosiderin

When and what to stain

- If clinical concern for a specific organism
  - Gram stain for bacteria
  - Silver stain for spirochetes
- If specific morphology is observed
  - Plasma cells -> cytomegalovirus IHC or silver stain
  - Peripheral funisitis -> GMS stain
  - Necrotizing funisitis -> silver stain

In summary thus far . . .

- Reviewed gross examination
  - What sections to take and why
- Inflammatory conditions
  - Where to look - what compartment
  - Why/what types of cells - etiology and impact
    - Neutrophils
    - Macrophages
    - Lymphocytes and plasma cells

A practical and algorithmic approach to evaluation of the placenta

Part 2

Soo-Jin Cho, MD, PhD
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UCSF
University of California
San Francisco

Conditions Associated with Adverse Outcome

- Acute chorioamnionitis with intense chorionic vasculitis
- Prolonged chorionic plate meconium with associated fetal vascular necrosis
- Villitis of unknown etiology with obliterative vasculopathy
- Fetal thrombotic vasculopathy
  - Pathologic umbilical cord lesions
Chronic Villitis

• Villitis of Unknown Etiology (VUE)
  – Maternal immune response to an unknown antigen in fetal villous stroma

• Infectious
  – TORCH infections

Distinction between VUE and Infectious Villitis

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Villitis of Unknown Etiology (VUE)

• Primarily T lymphocytes and histiocytes in villi
  – Occasional giant cells and a few neutrophils are permitted

• Range of involvement
  – More than a single focus (> 5 villi) of inflammation
  – Most severe is usually no more than 10% of placenta

Can you find the lesions?

Focus of chronic villitis

Chronic villitis and avascular villi
Other Features in Chronic Villitis

- **Patterns of involvement:**
  - Distal villi, 50%
  - Proximal stem villi with distal villi, 30%
    - Obliterative fetal vasculopathy
  - Basal villitis, 20% (30% B-cells)
    - Chronic deciduitis

- **Diffuse chronic villitis associated with diffuse perivillous fibrin deposition**
  - Increased risk of IUGR and prematurity
  - Recurrence in subsequent pregnancy

---

Inflammation? Yes → Villitis

- Clinical information:
  - 20-year-old, G1 P0 woman with a small for gestational age male infant and 318 gm placenta at 39 weeks gestation

- Gross description:
  - Approximately 25% of parenchyma is “dense fibrous appearing” and 5% focus of “apparent infarction”

---

Consult Case History

- Clinical information:
  - 20-year-old, G1 P0 woman with a small for gestational age male infant and 318 gm placenta at 39 weeks gestation

- Gross description:
  - Approximately 25% of parenchyma is “dense fibrous appearing” and 5% focus of “apparent infarction”
Stem villous vasculitis and chronic villitis
Mid cotyledon

Effects of vascular occlusion
Along basal plate

Effects of vascular occlusion

Final Diagnosis

• Patchy chronic villitis (villitis of unknown etiology) with obliterative fetal vasculopathy

Non-inflammatory Conditions

• Fetal thrombotic vasculopathy / chronic fetal vascular obstruction

• Maternal vascular underperfusion
  – Prototype: Pre-eclampsia
Fetal Thrombotic Vasculopathy

• Causes:
  – Circulatory stasis
  – Vascular injury
  – Hypercoagulability

Placental Reaction Patterns in FTV

• Distal villus lesions
  – Uniformly avascular villi
  – Villus stromal-vascular karyorrhexis
  – VUE with obliterative fetal vasculopathy

• Large fetal vessel lesions
  – Thrombosis
  – Intimal fibrin cushion
  – Recent
  – Remote

Uniformly avascular villi

• ≥ 3 foci of ≥ 2 terminal villi showing total loss of villous capillaries and bland hyaline fibrosis of the villous stroma in a distribution consistent with obstructed flow in large supplying or draining vessels
  – A small amount of karyorrhectic debris allowable

Villous stromal-vascular karyorrhexis

• ≥ 3 foci of ≥ 2 terminal villi showing karyorrhexis of fetal cells (nRBC, leukocytes, endothelial, and/or stromal cells) with preservation of surrounding trophoblast
  – Villi may also show stromal hypercellularity and mineralization
  – Villi can be hypovascular or show only capillary degenerative changes
  – Entrapped RBC and RBC fragments often seen
Where is the lesion?

Uniformly vascular villi

Diagnostic Options

<table>
<thead>
<tr>
<th></th>
<th>&lt;w/ chronic fetal vascular obstruction</th>
<th>Fetal thrombotic vasculopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformly avascular villi or villous stromal-vascular karyorrhexis</td>
<td>&gt;2 foci</td>
<td>&gt;2 foci or average of ≥15 affected vili/slide</td>
</tr>
<tr>
<td>Fetal vessel lesions</td>
<td>+/-</td>
<td>+/-</td>
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Placental Reaction Patterns in FTV

- Distal villus lesions
  - Uniformly avascular villi
  - Villus stromal-vascular karyorrhexis
  - VUE with obliteratorive fetal vasculopathy

- Large fetal vessel lesions
  - Thrombosis
  - Intimal fibrin cushion
    - Recent
    - Remote

Chorionic plate non-occlusive thrombi

Stem villi thrombi
Potential Causes

• **Circulatory stasis:**
  – Umbilical cord compression
    • Nuchal cord loops, loops around other fetal body parts, true knots
    • Hypercoiling, decreased Wharton’s jelly (< 8 mm diameter), marginal and membranous insertion
  – Right-sided heart failure
  – Polycythemia

Potential Causes (cont.)

• **Vascular injury**
  – Infection, meconium exposure, or HEV

• **Hypercoagulability**
  – Maternal diabetes, antiplatelet antibodies, or antiphospholipid syndrome
  – Abnormalities of fetal coagulation or homocysteine pathways

Non-inflammatory Conditions

• **Fetal thrombotic vasculopathy**

• **Maternal vascular underperfusion**
  – Prototype: Pre-eclampsia

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**Umbilical coiling index**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Hypocoiled</th>
<th>Mean ± SD</th>
<th>Hypercoiled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.1</td>
<td>0.21 ± 0.10</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypercoiled</td>
<td>0.25</td>
<td>0.16 ± 0.09</td>
<td>0.17 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>0.35</td>
<td>0.18 ± 0.12</td>
<td>0.18 ± 0.12</td>
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<tr>
<td></td>
<td>0.40</td>
<td>0.17 ± 0.13</td>
<td>0.17 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>0.45</td>
<td>0.28 ± 0.08</td>
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</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.20 ± 0.1</td>
<td>0.20 ± 0.1</td>
</tr>
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</table>

Normal coiling index is 1 coil/5 cm = 0.2
Hypercoiled is a coiling index of >0.35-0.45

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Features in Pre-Eclampsia

- **Decidual vasculopathy**
  - Mural hypertrophy of membrane arteriolar wall
  - Mean wall diameter > 30% of overall vessel diameter
  - Persistence of muscularized arteries in basal plate
  - Acute atherosis of decidual arteries
    - Fibrinoid necrosis of vessel wall + foam cells

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- **Decidual vasculopathy**
  - Mural hypertrophy of membrane arteriolar wall
  - Mean wall diameter > 30% of overall vessel diameter
  - Persistence of muscularized arteries in basal plate
  - Acute atherosclerosis of decidual arteries
  - Fibrinoid necrosis of vessel wall + foam cells

- **Increased placental site giant cells**
  - Numerous trophoblastic giant cells (> 2 nuclei) in the deep basal plate surrounded by decidua, not intermediate trophoblast or fibrinoid

- **Immature intermediate trophoblast**
  - Tightly cohesive, sheets or clusters of > 10 eosinophilic or vacuolated immature trophoblasts in the superficial basal plate

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**Syncytial Knots**

- **Definition:**
  - Count central portion of placenta, villi not touching
  - Multilayered aggregate of ≥ 5 syncytiotrophoblastic nuclei protruding from villous surface
  - Average of 28% of terminal villi with syncytial knots in term placenta (37-40 weeks)

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**Features in Pre-Eclampsia**

**Terminology**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Increased syncytial knots</td>
<td>Aggregates of syncytiotrophoblastic nuclei excessive for gestational age</td>
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<tr>
<td>Distal villous hypoplasia</td>
<td>Distal villi decrease in number, size and branching in the center of the lobule</td>
</tr>
<tr>
<td>Increased intervillous fibrin</td>
<td>Abnormal amounts of intervillous fibrin (≥ 5% of terminal villi enveloped by fibrinoid) in the basal half of villous parenchyma, nonperipheral section</td>
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<td>Villous agglutination</td>
<td>Cluster of adherent villi by fibrin or bridging knots with degeneration, stromal fibrosis or karyorrhexis</td>
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**Features in Pre-Eclampsia**

**Villous and Intervillous Space**

- **Increased syncytial knots**
  - Aggregates of syncytiotrophoblastic nuclei excessive for gestational age

- **Distal villous hypoplasia**
  - Distal villi decrease in number, size and branching in the center of the lobule

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  - Abnormal amounts of intervillous fibrin (≥ 5% of terminal villi enveloped by fibrinoid) in the basal half of villous parenchyma, nonperipheral section

- **Villous agglutination**
  - Cluster of adherent villi by fibrin or bridging knots with degeneration, stromal fibrosis or karyorrhexis

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**Tenney-Parker change**

**Intermediate infarct**
Clinical History and Final Diagnosis

- Severe pre-eclampsia at 33 weeks gestation
- Caesarean section
  - Baby girl with Apgars 8/9
  - 180 gm placenta

1. Small for stated gestational age.
2. Features consistent with history of pre-eclampsia; see comment.

Comment: List features seen such as decidual vasculopathy, Tenney-Parker change, and infarct (% parenchyma affected).

Differential Diagnosis of White Lesions on Gross Examination

- Thrombi
  - Subchorionic or intervillous
- Infarct
  - Early or remote
- Perivillous fibrin
- Avascular villi

Diagnosis?

Subchorionic thrombus

Perivillous fibrin – So What??

- Idiopathic disorder
  - Accumulation of fibrin and trophoblast-derived extracellular matrix around distal villi
- Within normal limits
- Increased perivillous fibrin
  - ≥ 5% of terminal villi enveloped by fibrinoid in the basal ½ of villous parenchyma, nonperipheral section
- Massively perivillous fibrin deposition
  - > 30%
- Maternal floor infarct
  - Basal plate rind
Massive Perivillous Fibrin Deposition
Maternal Floor Infarct

- Affect pregnancy
  - Prematurity (26-60%)
  - Fetal growth restriction (24-100%)
  - Stillbirth (13-50%)
  - Increased risk of cerebral palsy
- Tendency to recur in subsequent pregnancy (12-78% of cases)
Perivillous fibrin and extravillous trophoblastic proliferation

Maternal floor infarct

Conclusion: Useful Take-home Points

- Reviewed anatomy and gross examination
- Systematic approach to select disorders
  - Inflammatory lesions
    - Acute chorioamnionitis – recognize early changes and fetal response
    - Meconium – recognize vascular smooth muscle injury
    - Villitis of unknown etiology – distinguish from infectious villitis
  - Non-inflammatory
    - Recognize pre-eclampsia
    - Massive perivillous fibrin deposition can recur
    - c/o chronic fetal vascular obstruction/fetal thrombotic vasculopathy results from several etiologies

Clinical History

- 38-year-old, G2 P1 woman at 32-3/7 weeks’ gestation, transferred for preterm contractions
- Fetal ultrasound:
  - Abnormally thickened placenta with cystic changes
  - Large cystic mass in abdomen protruding through ventral hernia, enlarged kidneys, and cystic liver

Dilation of surface vessel—“cirroid” aneurysm

Enlarged cystic villi
Final Diagnosis: Mesenchymal Dysplasia

- Rare disorder of unknown etiology
  - Most are diploid
  - Possible theory of origin is confined placental mosaicism
- Fetus
  - Female preponderance (F:M = 3.6:1)
  - 20-30% of cases are associated with Beckwith-Wiedemann syndrome (macrosomia, omphalocele, macroglossia, visceromegaly)

Placenta in Mesenchymal Dysplasia

- Large for stated gestational age
  - Weight > 90th percentile
- Dilated and tortuous chorionic plate vessels
  - Fibromuscular hyperplasia +/- thrombi
- Large, edematous, cystic villi
  - Dilated stem villi lacking trophoblastic proliferation

Abnormal Products of Conception
A Practical Approach to Exclude Early Molar Pregnancy

Two different patients: 8 week products of conception

Which one is the complete mole?

Second Trimester Mole

Ultrasound Findings
- Classical

Microscopic Findings
- Classical
**First Trimester Mole**

**Ultrasound Findings**

- D&C

**Microscopic Findings**

- Abnormal, but not definite for mole

  - Missed / incomplete miscarriage
  - Cytogenetic disorder
  - Early mole

- Abnormal, but not definite for mole

  - Hydropic abortus
  - Cytogenetic disorder
  - Early mole

**Evaluation of Early Gestation Abnormal Villi**

- Morphology alone is not good enough

  - 20% to 30% are misclassified by academic experts

- Gold standard: Tests based on molecular definition

**Evaluation of Early Gestation POC Specimens**

- Morphology of Villi

  - Normal
  - Abnormal

- Ancillary Diagnostic Tests

  - Hydropic Abortus
  - Cytogenetic Disorder
  - Early Mole

**Outline of Talk**

**Clinical Implications of a Mole**

**Defining Normal versus Abnormal Villi in Early POC**

**Tests to Work Up Abnormal Villi**

- p57 stain
- Ploidy testing
- Genotype testing

**Clinical Significance of a Mole**

**Possible Outcomes if Untreated** (Gestational Trophoblastic Disease)

- Regress spontaneously (~ 75%)
- Persist (~ 20%)
- Invade Myometrial Vessels / Lymphatics (~ 2%)
- Metastasize (~ 5%)
- Recur as Mole
- Recur as Choriocarcinoma
Management of Moles

Possible Outcomes of Mole (Gestational Trophoblastic Disease)

- Histology alone is **not** fully predictive
- But clinical factors are predictive

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;=40</th>
<th>&gt;40</th>
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<tbody>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
</tr>
<tr>
<td>Months from pregnancy</td>
<td>&lt;=6</td>
<td>6-7</td>
</tr>
<tr>
<td>Serum HCG</td>
<td>&lt;=10^10</td>
<td>10^11-10^12</td>
</tr>
<tr>
<td>Tumor size</td>
<td>&lt;=3 cm</td>
<td>3.5-5 cm</td>
</tr>
<tr>
<td>Metastasis site</td>
<td>Lung</td>
<td>Spleen/ Kidney</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>0</td>
<td>1-4</td>
</tr>
<tr>
<td>Prior chemotherapy failure</td>
<td>-</td>
<td>-</td>
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WHO Prognostic Score for GTD

- Up to 7 points  **Low Risk**
- 8 points or more  **High Risk**

Management of Moles (UCSF)

- Serial Serum HCG
  - Serum HCG Normalizes
  - Serum HCG Plateau or Rises
- Contraception For 1 year
- Low WHO Risk Score
- High WHO Risk Score
- Single Agent Chemotherapy Methotrexate
- Multi Agent Chemotherapy EMA/CO

Consequences of “Over” Diagnosis of Mole

For Women receiving Assisted Reproductive Therapy

- 1 year of contraception
- Unnecessary exposure to chemotherapy

Confounding issue in these patients:

In this age range (>40 yrs):
- Higher rates of cytogenetic abnormalities
- Cytogenetic abnormalities may mimic early mole

Outline of Talk

Clinical Implications of a Mole

Defining Normal versus Abnormal Villi in Early POC

Tests to Work Up Abnormal Villi

- p57 stain
- Ploidy testing
- Genotype testing
Triad of Criteria to Examine in Villi

1. Architecture
2. Trophoblast Proliferation
3. Trophoblast Atypia

Villous Architecture

<table>
<thead>
<tr>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Term Placenta</th>
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<tbody>
<tr>
<td>6 weeks, normal karyotype</td>
<td>7 weeks, normal karyotype</td>
<td>9 weeks, normal karyotype</td>
</tr>
</tbody>
</table>
Normal Early Villous Trophoblast  
*Polar Proliferation*

6 weeks, normal karyotype  
No atypia of trophoblast

**Evaluation of Early Gestation POC Specimens**

- **Morphology of Villi**
  - Normal
  - Abnormal
  - Hydropic change
  - Mole
  - Cytogenetic disorder

**Implantation Site @ 6 weeks**

**Evaluation of Early Gestation POC Specimens**

- **Morphology of Villi**
  - Normal
  - Abnormal
  - Architecture
  - Trophoblast
    - Proliferation
    - Atypia

**Early Spontaneous Abortion**

- Early findings in villi (days):
  - Normal
  - Edema
  - Myxoid degeneration
  - Fibrosis / sclerosis / avascularity

- Later findings in villi (weeks):
  - Fibrosis / sclerosis / avascularity

- Decidual Pathology:
  - Inflammation / degeneration / necrosis
Hydropic Villi
Continuous spectrum of sizes

Hydropic Villi
Cisterns may occur

Morphology of Classic Complete Mole

Architecture
- Uniformly large
- Central cisterns (non-lined empty cavities)

Trophoblast Proliferation
- Exuberant
- Circumferential

Trophoblast Atypia
- Common

Complete Mole: Second Trimester

Uniformly Large Villi

Cisterns: Non-lined spaces due to edema/degeneration
Trophoblast Proliferation: Circumferential & Exuberant

- Solid Pattern
- Lace-like Pattern

Complete Mole
Trophoblast Proliferation

- Finger-like Pattern
- Mixed Patterns

Trophoblast Atypia

- Mimics Choriocarcinoma
- Do not diagnose choriocarcinoma if chorionic villi are present
- Trophoblast atypia does not predict behavior in moles
**Histology of Early Complete Mole**

**Architecture**
- Slightly large
- +/- central cisterns
- **Bulbous contours**
  - “knuckle-like” or “cauliflower-like”
- Hypercellular stroma
- Myxoid blue stroma
- **Karyorrhexis in stroma**

**Trophoblast Proliferation**
- Similar to classic complete mole

**Trophoblast Atypia**
- Similar to classic complete mole

---

**Early Complete Mole**

**“Soft sign” for Early Complete Mole:**
Karyorrhectic debris in villous mesenchyme

---

**Morphology of Partial Mole**

**Architecture**
- Dual population
  1. Large irregular villi, “scalloped contour”
  2. Small fibrotic/hypercellular villi
- Invagination of trophoblast surface
- Inclusions of trophoblast
- +/- central cisterns

**Trophoblast Proliferation**
- Patchy/focal
- Finger-like projections, tufts

**Trophoblast Atypia**
- +/-
Non-Molar Abnormal Villus Morphology

**Definition**
Non-molar gestation with abnormal villi
- Abnormal Villus Architecture
- Limited trophoblast proliferation
- Less severe than "classic" mole
- Overlap with "early" mole

**Cause**
- Unknown
- Some have cytogenetic disorders
  - e.g. trisomies, monosomies
Outline of Talk

Clinical Implications of a Mole

Defining Normal versus Abnormal Villi in Early POC

Tests to Work Up Abnormal Villi in Early POC

- p57 stain
- Ploidy testing
- Genotype testing

Moles are Defined by their Genotype

2 Components of Genotype

- Ploidy
- Parental contributions of DNA

Origin of Term “Ploidy” = Greek

“haploos”
- single

“diploos”
- double

Ploidy = Number of sets of chromosomes

<table>
<thead>
<tr>
<th>Haploid</th>
<th>Diploid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 set</td>
<td>2 sets</td>
</tr>
</tbody>
</table>

Normal gamete (sperm or oocyte)

Normal zygote

Fetus

Sets of chromosomes

<table>
<thead>
<tr>
<th>Sets of chromosomes</th>
<th>from Father</th>
<th>from Mother</th>
<th>Ploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-molar gestation (including cytogenetic disorders)</td>
<td>1</td>
<td>1</td>
<td>Biparental diploid</td>
</tr>
<tr>
<td>Complete mole</td>
<td>2</td>
<td>0</td>
<td>Diandric diploid</td>
</tr>
<tr>
<td>Partial mole</td>
<td>2</td>
<td>1</td>
<td>Diandric triploid</td>
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<td>Partial mole</td>
<td>2</td>
<td>1</td>
<td>Diandric triploid</td>
</tr>
</tbody>
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**Genetics of Complete Mole**

- **Monospermic**: 23,X
- **Dispermic**: 23,X 23,X
- **Dispermic**: 23,X 23,Y

Empty egg → 46,XX Mole

- **Non-viable**

---

**Can We Tell if DNA from Mother is Missing?**

- **Imprinted Genes**: One Parent's Gene is Always Silenced
  - **Paternal**
  - **Maternal**

  - **p57 is Imprinted**: Only Maternal p57 Gene Expressed

  - **Gene**

  - **Paternal**
  - **Maternal**

  - **p57 Protein Expression**

---

**Sets of chromosomes from Father and Mother**

<table>
<thead>
<tr>
<th></th>
<th>from Father</th>
<th>from Mother</th>
<th>p57 expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-molar gestation</td>
<td>1</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>(including cytogenetic disorders)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete mole</td>
<td>2</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>Partial mole</td>
<td>2</td>
<td>1</td>
<td>Yes</td>
</tr>
</tbody>
</table>

---

**p57 in Hydropic Abortus**

- Positive Villus Cytotrophoblast
- Positive Villus Mesenchyme
Maternal Decidua is always p57 Positive

**Sets of chromosomes**

<table>
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<tr>
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</tbody>
</table>

**Tests for Ploidy in Formalin Fixed Tissue**

- Traditional test: DNA Ploidy test (flow cytometry)
- New test: STR Genotype test (PCR)
Traditional Ploidy Test

Diploid = not partial mole

Triploid = Could be partial mole

Triploidy Alone is Not Diagnostic of Partial Mole

Digynic triploid gestations do not show either:

- Molar histology
- Molar behavior

\[ 23, X + 46, XX = 99, XXX \]

Redline R. Human Pathology 1998; 29: 505

Disadvantages of Traditional Test for Ploidy

Cannot distinguish:

- Di-andric versus di-gynic triploidy
  - May result in false positive diagnosis of partial mole
- Monospermic versus dispermic mole
  - Lose prognostic value of identifying dispermic moles
  - Dispermic moles thought to have higher recurrence risk

STR Genotyping Test for Products of Conception

- equivalent to “Paternity” testing, DNA fingerprinting
- PCR-based test (works in formalin fixed tissue)
- compares DNA in villi to DNA in maternal tissue
- specifically evaluates short tandem repeats (STR)

- STR are repeating units of 2 to 6 base pairs (e.g. GT, GT, GT)
- STR are polymorphic: many possible numbers of repeating units
- STR are heritable and stable

Polymorphism of STR:

Example of an STR (base pairs A,G,A,T) at a given location:

<table>
<thead>
<tr>
<th>Allele</th>
<th>Repeat Units</th>
<th>DNA Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 units</td>
<td>AGAT – AGAT</td>
</tr>
<tr>
<td>2</td>
<td>3 units</td>
<td>AGAT – AGAT – AGAT</td>
</tr>
<tr>
<td>3</td>
<td>5 units</td>
<td>AGAT – AGAT – AGAT – AGAT – AGAT</td>
</tr>
</tbody>
</table>

Normal individuals: 2 alleles at each STR locus
15 STR Loci are Compared in Villi versus in Maternal Tissue

<table>
<thead>
<tr>
<th>LOCUS</th>
<th>SIZE (#ALLELE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2S1338</td>
<td>307-359(14)</td>
</tr>
<tr>
<td>TPOX</td>
<td>222-250(8)</td>
</tr>
<tr>
<td>D3S1358</td>
<td>112-140(8)</td>
</tr>
<tr>
<td>FGA</td>
<td>215-355(28)</td>
</tr>
<tr>
<td>D5S818</td>
<td>134-172(10)</td>
</tr>
<tr>
<td>CSF1PI</td>
<td>304-341(10)</td>
</tr>
<tr>
<td>D7S820</td>
<td>255-291(10)</td>
</tr>
<tr>
<td>D8S1179</td>
<td>120-170(12)</td>
</tr>
<tr>
<td>TH01</td>
<td>169-202(10)</td>
</tr>
<tr>
<td>vWA</td>
<td>145-207(14)</td>
</tr>
<tr>
<td>D13S317</td>
<td>217-245(8)</td>
</tr>
<tr>
<td>D16S539</td>
<td>253-293(9)</td>
</tr>
<tr>
<td>D18S51</td>
<td>262-345(23)</td>
</tr>
<tr>
<td>D19S433</td>
<td>102-195(15)</td>
</tr>
<tr>
<td>D21S11</td>
<td>185-240(24)</td>
</tr>
<tr>
<td>Amelogenin</td>
<td>107/113(X/Y)</td>
</tr>
</tbody>
</table>

DNA extracted from tissue on slide scraped from:

- **Villi**
  - Biparental Diploid
  - Non-molar

- **Decidua**
  - Diandric Diploid
  - Complete Mole (Monospermic)

Maternal Tissue (Decidua)

Chorionic Villi

Maternal Tissue (Decidua)

Chorionic Villi

Diandric Triploid

Partial Mole (Dispermic)

Maternal Tissue (Decidua)

Chorionic Villi

Diandric Triploid

Non-molar
Limitations of STR Genotyping for POC

- Currently only a few labs offer the test
- Requires maternal tissue (decidua or any other tissue)
- DNA contamination is a problem if villi and decidua are too intermixed on slide to scrape off separately
- Donor egg pregnancies will simulate complete mole
  - We recommend always doing p57 staining
- Not designed to detect cytogenetic disorders

Evaluation of Early Gestation POC Specimens

Morphology of Villi

Normal → Abnormal

p57 + Genotyping

Evaluation of Early Gestation POC Specimens

Morphology of Villi

Normal - - - Sort of - - - Sort of - - - Abnormal

Normal   Abnormal

?    ?

p57 + Genotyping

What amount/degree of “abnormal” is enough to merit testing?
Evaluation of Early Gestation POC Specimens

Morphology of Villi

Normal - - - Sort of - - - Sort of - - - Abnormal

Normal

Abnormal

Decision based on individual experience

p57 + Genotyping

My Personal Threshold for Ordering Testing

If any 2 or more features are present:

Architecture

Invaginations, inclusions, protrusions

Karyorrhexis

Trophoblast

Patchy proliferation

Lace-like pattern

Atypical trophoblast

Present

Outline of Talk

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