Placental Potpourri: the Pernicious, Picayune, and Pervasive

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Outline of This Talk

• Value of placental examination
• Brief review of placental circulation, histology
• Lesions that impact neonatal or maternal health
  • Intrauterine infection
  • Villitis of unknown etiology
  • Fibrin deposition
  • Other circulatory disorders
  • Fetal thrombotic processes
Value of Placental Examination

- Etiology of intrauterine or perinatal death
- Etiology of preterm delivery
- Etiology of anomaly
- Etiology of neurologic impairment
- Alter management of future pregnancies
- Pathophysiology of maternal or neonatal disorders
- Useful in the care of a sick neonate
Etiology of Stillbirth

• Classic study of perinatal autopsies
  • 92% of cases had placental abnormalities
  • In one-third cause of death involved placenta or cord
  • 16% placenta or cord contributed to death

Etiology of Stillbirth

Cause of death (COD) determination in structurally normal stillbirths

- Increased from 38.5% to 79.5% (p<.0001) after policy of placental examination instituted
- Placental exam provided
  - Confirmation of COD in 24.6%
  - New diagnostic information and COD in 44.7%
  - No additional info in 30.7%

Wu X et al. Mod Path 2009;22(sup 1):10A poster 33
Value of Placental Examination

- Etiology of intrauterine or perinatal death
- Etiology of preterm delivery
- Etiology of anomaly
- Etiology of neurologic impairment
- Alter management of future pregnancies
- Pathophysiology of maternal or neonatal disorders
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Pathogenesis of Intrauterine Infection

- Ascending - typically bacterial → chorioamnionitis
- Transplacental - viral, protozoal, bacterial → villitis
Ascending Infection

- Most common type of infection
- Organisms enter through cervix
- Relationship with rupture of membranes
- Inflammation of fetal membranes and umbilical cord
- Neonatal pneumonia, sepsis by swallowing, aspirating infected amnionic fluid
Intrauterine Infection

Common
- See in 10% to 20% of term deliveries
- Up to two-thirds of preterm deliveries

Important associations
- Preterm delivery
- Neonatal sepsis
- Cerebral palsy
- Chronic lung disease
Chorioamnionitis

- At term - related to presence and duration of membrane rupture
- Preterm - likely precedes and *causes* membrane rupture
  - inflammatory response produces
    - prostaglandins, cytokines - trigger labor
    - metalloproteinase - weaken membrane integrity, remodel cervical tissue
Intrauterine Infection

- Prematurity is leading cause of perinatal morbidity and mortality in the US
  - 70% of neonatal deaths
  - 50% of cases of cerebral palsy
  - Chronic lung disease, mental retardation
- Amnionic infection is a major cause of preterm deliveries
Fetal Inflammatory Response Syndrome

- Intrauterine infection leads to production of inflammatory cytokines by fetus
- Inflammatory response correlates with adverse outcomes
  - Neonatal sepsis
  - Pneumonia
  - Bronchopulmonary dysplasia, RDS
  - Intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy
  - Necrotizing enterocolitis
Fetal Inflammatory Response Syndrome

- UC IL-6 and AF IL-6 correlate with CP and periventricular leukomalacia
- Acute funisitis, especially arteritis, may be better predictor of CP than IL-6 levels
- Severe fetal outcomes occur more often in infants with arteritis
- True after adjusting for gestational age

Cerebral Palsy and Chorioamnionitis

• Infection and inflammation do not explain all cases of CP

• Other possible cofactors
  • Gestational age at time of infection
  • Intensity of fetal response
  • Genetic differences in genes that code cytokines
Cerebral Palsy and FIR Syndrome

Role of cytokine polymorphisms

- Mannose binding lectin-221, TNF-α-308 and MBL-52, 54, 57
- These polymorphisms alter levels of circulating cytokines
- Any of these polymorphisms increased risk of CP
- Any MBL 54- ↑ risk of diplegia
- Heterozygous TNFα - ↑ risk of quadraplegia at term
- Heterozygous or homozygous TNFα  - ↑ risk of hemiplegia at <32 weeks

Cerebral Palsy and FIR Syndrome

Possible mechanisms

- Direct toxicity to neurons
- Impair transition from oligo precursors to mature oligos
- Activate endothelial cells, shift to prothrombotic state, ? Synergism with thrombophilic polymorphisms
- ↑ permeability of blood brain barrier
- ↓ innate response to infection
Proposed Pathogenesis

Bacterial infection ➔ ↑ cytokines

↑ Permeability of blood brain barrier ➔ ↑ passage of bacteria, cytokines

Cell destruction, abnormal proliferation
Chronic Lung Disease and FIR Syndrome

- Bronchopulmonary dysplasia (BPD) not explained by prematurity alone
- Very LBW infants with BPD
  - ↑ incidence of chorioamnionitis
  - ↓ respiratory distress
- BPD correlates with ↑ antenatal cytokines
- Infants with highest IL-6, IL-8, IL-1 levels had highest risk of BPD, controlled for gestational age
- Animal models – cytokines disrupt lung development by variety of mechanisms

Yoon BH et al. Am J Obstet Gynecol 1997; 177-825
Fetal Inflammatory Response

Chorioamnionitis and funisitis

- Presence correlates with outcomes
- Severity correlates with outcomes
- Numerous staging and grading systems
  - All have shortcomings
  - Reproducibility not perfect
  - Lack of prospective correlation with outcomes
Better standardization of diagnostic terminology is needed

- Degree, location of inflammation related to outcome
- Stratification of prognosis
- Stratification of treatment
- Facilitate studies between institutions

Redline RW et al. have proposed a scheme for staging and grading the maternal and fetal response

Ascending Infection

- Maternal response – acute chorioamnionitis
  - In free membranes neutrophils emigrate from decidual vessels through chorion and amnion
  - In placenta neutrophils emigrate from intervillous space through chorion and amnion
- Fetal response – funisitis, chorionic vasculitis
  - Neutrophils emigrate from umbilical vessels
  - Neutrophils emigrate from chorionic vessels
Maternal Inflammatory Response
Stage 1

• Suggested diagnostic terminology
  • Acute subchorionitis or early acute chorionitis

• Definition
  • Neutrophils in subchorionic fibrin and/or membranous trophoblast

Maternal Inflammatory Response
Stage 1 - Acute Chorionitis

Neutrophils in membrane trophoblast
Maternal Inflammatory Response
Stage 1 - Early Acute Chorionitis

Neutrophils in fibrin beneath chorionic plate
Maternal Inflammatory Response
Stage 2

- Suggested diagnostic terminology
  - Acute chorioamnionitis

- Definition
  - Neutrophils in chorionic plate or membranous chorionic connective tissue and/or amnion

Maternal Inflammatory Response Stage 2 – Acute Chorioamnionitis

Scattered neutrophils in chorion and amnion
Maternal Inflammatory Response
Stage 3

• Suggested diagnostic terminology
  • Necrotizing chorioamnionitis
• Definition
  • Neutrophil karyorrhexis, amnion necrosis and/or amniotic basement membrane thickening/hypereosinophilia

Maternal Inflammatory Response
Stage 3

Neutrophils with karyorrhexis
Maternal Inflammatory Response Stage 3 – Necrotizing Chorioamnionitis

Amniotic epithelial necrosis; thickened, eosinophilic basement membrane
Maternal Inflammatory Response
Grade 1 – Mild-Moderate

• Suggested diagnostic terminology
  • Mild or moderate

• Definition
  • Individual or small clusters of neutrophils

Maternal Inflammatory Response
Grade 1 - Mild-Moderate

Scattered neutrophils
Maternal Inflammatory Response
Grade 2 - Severe

• Suggested diagnostic terminology
  • Severe acute chorioamnionitis or with subchorionic microabscesses

• Definition
  • Confluent neutrophils between chorion and decidua; ≥ or equal to 3 isolated foci or continuous band

Maternal Inflammatory Response
Grade 2 - Severe

Confluent band of neutrophils
Fetal Inflammatory Response Stage 1

- Suggested diagnostic terminology
  - With chorionic vasculitis or umbilical phlebitis
- Definition
  - Intramural neutrophils in chorionic vessels and/or umbilical vein

Fetal Inflammatory Response
Stage 1 - Phlebitis

Neutrophils in smooth muscle of umbilical vein wall
Fetal Inflammatory Response
Stage 1 - Chorionic Vasculitis

Neutrophils in wall of large chorionic vessels on fetal plate
Fetal Inflammatory Response
Stage 2

• Suggested diagnostic terminology
  • With umbilical vasculitis (one or both arteries +/- vein) or umbilical panvasculitis (all vessels)

• Definition
  • Intramural neutrophils in umbilical artery or arteries (+/- vein)

Fetal Inflammatory Response
Stage 2 - Arteritis

Neutrophils in smooth muscle of wall of umbilical artery
Fetal Inflammatory Response
Stage 3

• Suggested diagnostic terminology
  • With necrotizing funisitis or with concentric umbilical perivasculitis

• Definition
  • Neutrophils +/- debris in concentric bands-rings-halos around one or more umbilical vessels

Fetal Inflammatory Response
Stage 3 - Necrotizing Funisitis

Neutrophils and debris ring the umbilical vessels
Fetal Inflammatory Response
Stage 3 - Necrotizing Funisitis
Fetal Inflammatory Response
Grade 1 - Mild-Moderate

- Suggested diagnostic terminology
  - Mild – moderate
- Definition
  - Scattered neutrophils

Fetal Inflammatory Response
Grade 2 - Severe

• Suggested diagnostic terminology
  • With a severe fetal inflammatory response or with intense chorionic (umbilical) vasculitis

• Definition
  • Near confluent intramural neutrophils in chorionic and/or umbilical vessels with attenuation/degeneration of vascular smooth muscle
Chorionic Vasculitis with Thrombi
Chorionic Vasculitis with Thrombi
Chorionic Vasculitis with Thrombi
Ascending Infection

- Rarely see causative organisms in sections
- Exceptions:
  - Group B beta-hemolytic *streptococcus*
  - *Fusobacterium*
  - *Candida*
Group B beta-hemolytic *strep*

Bacterial colonies with no inflammatory response
Hematogenous Infection

- Virus – CMV, Rubella, Varicella, Parvovirus, HSV
- Bacteria – Treponema pallidum, Listeria
- Parasites – Toxoplasma gondii
- Unknown – > 95%, ? abnormal immune reaction
Hematogenous Infection
Clinical Impact

• Spontaneous abortion – Rubella
• Fetal death in utero, stillbirth – Parvovirus
• Malformations – Rubella, Toxo
• Active infection – Toxo, CMV
• Delayed sequelae – CMV and others
  • Deafness
  • Mental retardation
  • Learning disabilities
<table>
<thead>
<tr>
<th>Type</th>
<th>acute, chronic, granulomatous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>lymphs, histiocytes, plasma cells, neutrophils</td>
</tr>
<tr>
<td>Necrosis</td>
<td>necrotizing, non-necrotizing</td>
</tr>
<tr>
<td>Distribution</td>
<td>focal, diffuse, basal</td>
</tr>
<tr>
<td>Severity</td>
<td>very mild, mild, mod, severe</td>
</tr>
</tbody>
</table>
Villitis

Collections of abnormally agglutinated villi
Villitis

Non necrotizing villitis
Villitis

Granulomatous villitis
Villitis

Basal villitis
Villitis

• > 95% is villitis of unknown etiology (VUE)
• Certain features do point to infections as the etiology
  • Clinical history
  • Active, resolving, healed areas
  • Prominent fibrosis
  • Often associated acute chorioamnionitis
• Specific features
Infectious Villitis

Confirm with

• Special stains
• Molecular techniques
• Maternal/infant serology
• Detailed clinical history
Congenital CMV Infection

0.2% to 2.5% of live births

- 5% to 10% have disseminated disease
- 90% unrecognized at birth
  - 5% to 15% have long-term effects
    - Mental retardation
    - Learning disabilities
    - Sensorineural hearing loss
Congential CMV Infection

• In utero > intra partum, post partum
• Caused by 1º or 2º infection
• If 1º more likely:
  • Symptomatic
  • Late sequelae
• Treatment immediately after birth may decrease severity of neurologic damage
Congenital CMV Infection

- Recent evidence that decidual cells or decidual macrophages are reservoir for CMV
- Reactivation is more likely after inflammatory response to bacterial infections
Congenital CMV Infection

- Usually infected women are asymptomatic
- No guidelines for treating CMV during pregnancy
- Role of screening pregnant women for CMV is unclear
CMV Placentitis

- Lymphoplasmacytic villitis
- Necrotizing vasculitis
- Vessel occlusion
- Stromal hemosiderin
- Viral inclusions – 20%
CMV

Necrotizing villitis
Numerous plasma cells – important clue to CMV
CMV

Vascular sclerosis
CMV

Vascular sclerosis
CMV

Stromal sclerosis
CMV

Stromal hemosiderin and sclerosis
CMV

Inclusions in stromal cells
CMV

Inclusions in endothelial cells
CMV

Eosinophilic nuclear and basophilic cytoplasmic inclusions
CMV
CMV Placentitis

Immunohistochemistry, in situ hybridization and PCR will detect CMV in cases of congenital infection

- When placenta is normal
- When infection is sub clinical
Villitis of Unknown Etiology

- Accounts for majority of villitis
- Incidence
  - 6% to 26% of placentas
  - Usually greater than 32 weeks gestation
- No gross abnormalities
- 85% are focal
- Most randomly distributed
  - 20% have basal location
Villitis of Unknown Etiology

- Most cases are necrotizing
- Most are lymphohistiocytic
- Most cases are focal
- May be associated with vasculitis of fetal stem vessels
  - Avascular downstream terminal villi
Villitis of Unknown Etiology

Theories of pathogenesis

• Result of unidentified pathogen
• Immunologic phenomenon
Villitis of Unknown Etiology

- **Inflammatory cells**
  - Maternal
  - T helper cells
  - Ia antigen-bearing macrophages
- ↑ incidence in women with autoimmune disorders
- Tendency to recur
Villitis of Unknown Etiology

Clinical associations

Severity of clinical findings generally related to severity of villitis

- Small for gestational age infants
- Antenatal growth arrest
- Perinatal mortality
- Oligohydramnios without membrane rupture
- Chronic monitoring abnormalities
Villitis of Unknown Etiology

Which cases to work up for infection?

• Suspicious maternal history
• Suspicious clinical findings in neonate
• Not mild
• Pattern besides lymphohistiocytic
Villitis

Basic work up

• IHC for CMV
• IHC for toxoplasma
• Warthin-Starry or IHC for spirochetes
• Gram stain if lots of neutrophils or abscesses
Important Circulatory Disorders

• Abnormal fibrin deposition
  • Massive perivillous fibrin
  • Maternal floor infarct
• Infarction
• Retroplacental hematoma
Perivillous Fibrin

• See some fibrin in most placentas
• Grossly visible fibrin in 22%
  • Underneath chorionic plate
  • Around stem villi
  • Just above basal plate
• See less in preeclampsia (13%)
• See less in preterm (6%)
Normal Fibrin Deposition
Normal Fibrin Deposition

Above basal plate
Fibrin Deposition

Gross

• Firm, tan, yellow or white
• Fuzzy border
  • Interspersed red villous tissue
  • Not as well circumscribed as infarct
• Often in periphery
Perivillous Fibrin Deposition
Massive Perivillous Fibrin Deposition
Perivillous Fibrin Deposition

Not as well circumscribed as infarcts
Perivillous Fibrin Deposition

Expansion of intervillous space
Perivillous Fibrin Deposition

Cytotrophoblast proliferation
Perivillous Fibrin Deposition

Differential diagnosis

• Infarct
  • Also firm, white if not recent
  • Well circumscribed
  • Collapse, not expansion, of intervillous space
  • No trophoblast proliferation
• Maternal floor infarct
  • Involves the basal villi and decidua
Perivillous Fibrin Deposition

Clinically significant if:

- Entraps 20% of terminal villi
- Central-basal location

Clinical significance

- Intrauterine growth retardation
- Low placental weight
- Fetal death in utero

Redline RW, Patterson P. Arch Pathol Lab Med 1994; 18:698
Perivillous Fibrin Deposition

Katzman and Genest

- Transmural massive fibrin deposition (MFD)
  - Extends from fetal to maternal surface
  - Entraps > 50% of villi on at least one slide
  - Rare - 0.28 to 0.5% of examined placentas

Pediatr Dev Pathol 2002;5:159-164
Perivillous Fibrin Deposition

Katzman and Genest

- 31% of infants had IUGR
- 14% had MFD or maternal floor infarct in other 2nd or 3rd trimester pregnancies
- 50% had MFD or maternal floor infarct in other 1st trimester pregnancies

Pediatr Dev Pathol 2002;5:159-164
Perivillous Fibrin

• Pathogenesis is unclear
• Likely related to stasis and thrombosis of maternal blood
Perivillous Fibrin

- Massive perivillous fibrin in small for gestational age (SGA) and prior SGA
- Preeclampsia, collagen vascular diseases, coagulopathy
- Aspirin, dipyridamole prevents perivillous fibrin and SGA

Fuke Y et al Gyn Obstet Invest 38:5-9, 1994
Maternal Floor Infarct
Maternal Floor Infarct
Maternal Floor Infarct
Maternal Floor Infarct

- Infarct is a misnomer - fibrinoid deposition
- Fibrinoid involves decidua basalis
- Encases adjacent villi
- Katzman and Genest definition
  - Basal villi of entire maternal floor be encased by fibrinoid at least 3 mm thick on at least one slide

Pediatr Dev Pathol 2002;5:159-164
Maternal Floor Infarct

- Stillbirth – 13% to 50%
- Growth retardation - 24 to 100%
- Preterm delivery – 26% to 60%
- Independent predictor of neurologic impairment in preterm infants
- Recurrence – 12% to 78%
Subchorionic Fibrin Deposition

Not clinically significant
Subchorionic Fibrin

Layers of blood and fibrin beneath chorionic plate
Subchorionic Fibrin

• Not clinically significant
• May reflect damage to fetal plate by fetal movements
• Less common in infants with disorders that restrict movement
Infarcts

Firm, well circumscribed, often pale
Infarcts

Well circumscribed
Usually abut the maternal surface
May be red, tan, or white
Extensive Infarction
Infarcts

Loss of intervillous space
Infarcts

Ghost villi with thick trophoblast membranes
Infarcts

Differential diagnosis

• Perivillous fibrin deposition
• Intervillous thrombohematoma
  • Also well circumscribes, white if not recent
  • Often laminated
• Contain no villi, only blood
Intervillous Thrombohematomata

Well circumscribed, laminated, red if early, white if older
Infarcts

Pathogenesis

• Decreased blood supply to group of villi
  • Vessel narrowing (hypertension)
  • Atherosis (preeclampsia)
• Physical separation (retroplacental hematoma)
Normal Vascular Remodeling

- Replacement of smooth muscle and elastic by fibrinoid material
- Vessels become flaccid, low resistance tubes
- Increases blood flow 10-fold
Decidual Vasculopathy

Two forms

- Lack of physiologic transformation
- Acute atherosis

Both are associated with

- Preeclampsia
- IUGR
- Small for gestational age infants
- Collagen vascular disease
Implantation Site Vessels

Prominent endovascular trophoblast
Acute Atherosis

Prominent fibrinoid necrosis, very narrow lumens
Acute Atherosis
Infarcts

Normal

- See in 10-25% of term placentas
- Small, located in periphery

Clinically significant if:

- Multiple, central
- Large (>3 cm)
- Preterm
Infarcts

Clinical significance for fetus

• Hypoxia
• Intrauterine growth restriction
• Periventricular leukomalacia (preterm)
• Intrauterine fetal demise
Infarcts

Clinical significance for the mother

• Extensive implies significant maternal disease
• Preeclampsia - severity related to extent of infarction
• Maternal thrombophilic conditions
Infarcts

- Sample areas away from infarcts
  - Determine overall perfusion of placenta
  - Small, narrow villi, few vessels, increased knots indicates poor perfusion
- Normally perfused placenta can lose ~20% of villi without harming infant
- Less reserve if already poorly perfused
Low Flow Changes

Small, thin, unbranched villi
Increased syncytial knots
Retroplacental Hematoma

Densely adherent clot indents surface, underlying infarction
Retroplacental Hematoma
Retroplacental Hematoma

Blood clot indents placenta, underlying infarction
Retroplacental Hematoma
Retroplacental Hematoma

Villous stromal hemorrhage may be seen beneath, especially in the 2nd trimester
Retroplacental Hematoma

Incidence ~ 5%

Clinical associations

• Preeclampsia
• Heavy smoking, cocaine
• Trauma
• Acute chorioamnionitis
• Maternal thrombophilic conditions
• Prior abruption
Retroplacental Hematoma

Postulated pathogenesis

- Atherosis (preeclampsia) – weakened vessels
- Cocaine, cigarettes – spasm
- Thrombophilia - thrombosis
Placental Abruption

A clinical syndrome

- Vaginal bleeding
- Increased uterine tone
- Uterine tenderness
- Decreased fetal heart tones
- Maternal hypotension, DIC
Retroplacental Hematoma

- 30% with abruption have hematoma
- 35% with hematoma have abruption
- Clinical significance
  - Depends on size, amount of infarction, how well rest of placenta is perfused
  - Fetal death
  - Periventricular leukomalacia (preterm)
Marginal Hematoma
Marginal Hematoma
Marginal Hematoma

- Blood clot located between disc edge and membranes
- Often associated with hematoma on membranes
- Occurs in placentas implanted close to os
- Causes bleeding during delivery
- Clinically mistaken for “abruption”
- Not clinically significant – no associated infarction
Circulatory Disorders

Disorders of maternal circulation

- Perivillous fibrin deposition
- Maternal floor infarct
- Infarct
- Intervillous thrombohematoma
- Retroplacental hematoma
- Marginal hematoma
Fetal Vascular Obstruction

May occur at any level

- Umbilical cord vessels
- Chorionic plate vessels
- Small vessels in villi
Fetal Vascular Obstruction

- Fetal circulation of placenta and of fetus itself are connected during gestation
- Vascular obstruction in fetal circulation of placenta may be associated with and serve as a marker for thrombotic or embolic lesions in circulation of fetus
Fetal Vascular Obstruction

Well circumscribed, pale but not firm
Fetal Vascular Obstruction
Fetal Vascular Obstruction

Well circumscribed area of pale, fibrotic villi
Fetal Vascular Obstruction
Fetal Vascular Obstruction

Thrombosis of larger vessels, downstream avascular terminal villi
Fetal Vascular Obstruction
Fetal Vascular Obstruction

Sclerosis of vessels in higher order villi, avascular terminal villi
Villous Stromal-Vascular Karyorrhexis

Karyorrhexis in fetal vessels, fragmented red cells
Chorionic Plate Vessel Thrombus with Calcification
Fetal Vascular Obstruction

Pathogenesis

• Stasis
• Hypercoagulability
• Vascular damage
Fetal Vascular Obstruction

Clinical Associations

• Maternal diabetes
• Maternal thrombophilia (but not fetal thrombophilia)
• Chorioamnionitis
Fetal Thrombotic Vasculopathy

Unanswered questions:

- Incidence from prospective data
- Predictive value
- Clinically significant amount
- Appropriate work up
- Role of treatment in next pregnancy
- Pathogenesis
Maternal Thrombophilic Conditions

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V mutation (Leiden)
- Prothrombin 20120A
- MTHFR C677T- hyperhomocysteinemia
Maternal Thrombophilic Conditions

Clinical associations

• Controversial
• Preeclampsia
• Late pregnancy loss
• Intrauterine growth restriction
Hereditary Thrombophilic Conditions

- Problems
  - Poor study design
  - Imprecise placental terminology
- May be associated with
  - ↑ number, ↑ size of infarcts
  - Acute atherosis, spiral artery thrombi
  - Retroplacental hematoma/abruption
  - Fetal vascular obstruction
Fetal Vascular Obstruction

- Cord abnormalities
  - Long cord
  - Velamentous insertion
  - Excess twisting
  - Nuchal cord
Fetal Vascular Obstruction

Consequences for fetus if extensive:

• Fetal growth restriction
• Chronic monitoring abnormalities
• Stillbirth
• Neurologic impairment
• Hepatic failure
• Vascular compromise involving kidneys, GI
Fetal Thrombotic Vasculopathy

84 consecutive perinatal autopsies

• 16 (19%) had avascular terminal villi
• extensive in all 16
• Involved 25 to 50% of placenta in 4
• 6 (37.5%) had fetal somatic thrombi
• 5/8 mothers had coagulation abnormalities

Kraus FT, Archeen V  Human Pathol 30:759, 1999
Fetal Thrombotic Vasculopathy

125 cases from children with neurologic deficits referred for litigation

- 4 vascular lesions significantly increased
  - Fetal thrombotic vasculopathy
  - VUE with obliterative fetal vasculopathy
  - Chorioamnionitis with fetal vasculitis
  - Meconium-associated vascular necrosis

Redline RW Am J Obstet Gynecol 2005; 192:452-7
Fetal Vascular Obstruction

- One or more of these seen in 51% of cases vs. 10% of controls
- 52% of CP patients had one of these lesions
- Cord abnormalities more common in infants with fetal thrombotic vasculopathy

Redline RW Am J Obstet Gynecol 2005; 192:452-7
Redline RW Hum Pathol 2004;35:1494-8
Placental Potpourri: the Pernicious, Picayune, and Pervasive
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The placenta is a remarkable organ. It undergoes rapid growth and profound changes in structure to supply the needs of the rapidly growing fetus for the crucial first 40 weeks of development. During life in utero, the circulation of the fetus and the circulation of the placenta form one continuous unit. Examination of the placenta, which is easily accessible, may provide valuable information about events during gestation affecting the fetus.

I’ll begin by discussing the importance of placental examination. The remainder of the talk will focus on those placental abnormalities that are clinically important for the infant, the mother or both. Some of these abnormalities are common but others are easily overlooked. Several have a risk of recurrence in subsequent pregnancy. Many represent areas where we have made important new discoveries in terms of pathophysiology with important implications for fetal and maternal health.

Why Examine the Placenta?

Placental examination can be very rewarding in determining the cause of an intrauterine or perinatal death; investigations of such deaths are incomplete without a placental examination. In a large, classic study of perinatal autopsies, placental abnormalities were found in 92% of cases. The cause of death was a placental or cord abnormality in almost a third of cases and in 16% of cases was a contributing factor. In more recent studies of structurally normal stillborn infants, examination of the placenta significantly increased the percentage of cases in which a cause of death could be determined.

Examination of the placenta may help explain the etiology of a preterm delivery, a congenital anomaly or other adverse neonatal outcome. Obstetrical management of subsequent pregnancies may be altered if conditions that show a risk of recurrence such as abruption, massive perivillous fibrin deposition, or maternal floor infarct are identified on placental examination. Information that may help explain the outcome of a neurologically impaired child and be useful in the legal defense of these cases may be obtained from placental examination. In a general way, examination of placentas has provided and will continue to provide insights into the pathophysiology of various important maternal and neonatal disorders potentially improving diagnosis and therapy for these conditions.

The information obtained from placental examination may be immediately useful in the care of a sick neonate and may be very helpful to parents and pediatricians caring for impaired children later in life. In order to maximize the value of placental examination, pathologists and informaticians need to develop better ways to ensure that the results of the placental examination reach and are understood by the neonatologists and general pediatricians caring for children and communicating with parents, in addition to the obstetrician who sent the placenta for examination. This is challenging because mothers and babies frequently have different last names and are often cared for in different hospitals.

Infection and the Placenta

Intrauterine infections can have important consequences for the fetus including abortion, stillbirth, active infection in the newborn period and long-term sequelae such as neurologic deficits including cerebral palsy, mental retardation, blindness, deafness and learning disabilities.
There are two broad patterns of placental infection - ascending infections and hematogenous infections, each associated with a characteristic type and pattern of inflammation within the placenta as well as characteristic organisms. In general, ascending infections, the most common pattern, are caused by bacteria that pass from the vagina or cervix into the uterus and cause acute inflammation of the fetal membranes (acute chorioamnionitis) and umbilical cord (acute funisitis). In hematogenous infections, a less common pattern, organisms are passed hematogenously from the mother to the placenta and fetus. This is the pattern typically seen in TORCH infections and may be caused by viral organisms (CMV, Rubella and others), protozoa (*Toxoplasma gondii*) and some bacteria (*Listeria monocytogenes*, *Treponema pallidum*). The placenta usually shows chronic inflammation of the villi (villitis) but may also have a component of chorioamnionitis. Infants may also be infected with bacterial or viral agents after passing through an infected birth canal, a common form of infection with HIV and HSV, but this form of transmission does not involve the placenta.

### Ascending Infection and Acute Chorioamnionitis

Chorioamnionitis is the most common form of inflammation in the placenta. It is found in the placentas of about 10 to 20% of term deliveries. Chorioamnionitis is strongly correlated with prematurity: about two-thirds of infants born before 24 weeks gestation will have evidence of chorioamnionitis. The prevalence is also increased in women of low socioeconomic status and African-American women. A distinction needs to be made between clinical and histologic chorioamnionitis. Clinical chorioamnionitis is characterized by some combination of fever, elevated maternal white count, premature rupture of membranes and foul vaginal discharge. The gold standard for diagnosis, however, remains histologic chorioamnionitis with the presence of neutrophils in the chorion and/or amnion. There is very poor correlation between the clinical diagnosis of chorioamnionitis and histologic chorioamnionitis; 72% of cases with histologic chorioamnionitis don’t meet the clinical diagnosis and 9% of cases with clinical chorioamnionitis don’t have histologic chorioamnionitis.

It is now clear that infection causes acute chorioamnionitis. The implicated organisms may be aerobic or anaerobic and are typically normal flora or gastrointestinal contaminants of the vagina and cervix. Factors such as rupture of membranes, cervical dilatation, and the presence of an IUD or cerclage may facilitate spread to the amniotic cavity. There is a strong relationship between rupture of membranes and chorioamnionitis, the risk of chorioamnionitis increasing with increasing duration of membrane rupture. This relationship is particularly strong at term. In other cases, chorioamnionitis may precede rupture of membranes actually causing premature rupture of membranes and/or preterm birth. The organisms seen in preterm labor with intact membranes are typically low virulence vaginal and enteric organisms. There is increasing evidence that some of these organisms may ascend from the lower GYN tract weeks or even months before acute chorioamnionitis develops and reside in the uterine tissues including the decidua due to decreased local immunity secondary to pregnancy.

### Pathologic Features and Grading of Acute Chorioamnionitis

The fetal membranes in chorioamnionitis are typically normal on gross examination but in cases of severe or longstanding infection, may be discolored, friable and foul smelling. Both the mother and the fetus (after about 20 weeks) respond to infection in the amniotic cavity. Maternal neutrophils first migrate from the intervillous space, which is essentially a maternal blood vessel, and accumulate in the fibrin layer beneath the chorion. From here they pass through the connective tissue of the chorion and eventually into the amnion of the fetal plate of the placenta in response to chemotactic factors generated by bacteria in the amniotic fluid.
Maternal neutrophils also migrate from maternal blood vessels in the decidua, through the
decidua, the chorion and eventually into the amnion of the free membranes (membrane roll).
Fetal neutrophils migrate out of large vessels on the chorionic plate (chorionic vasculitis) and
may also migrate from the umbilical cord vessels, typically first from the umbilical vein then by
the artery. Neutrophils are first seen in the clear spaces between smooth muscle cells but
eventually migrate completely through the vessel wall to involve the surrounding Wharton’s
jelly. If severe, rings or arcs of degenerating neutrophils will surround the umbilical vessels.

Typically, causative organisms are not seen on histologic sections. Important exceptions
include Group B streptococcus, Candida and fusobacterium. When organisms are identified, it is
important to consider post delivery overgrowth in unfixed specimens, especially those without
inflammation.

Because of the increasingly clear relationship between acute chorioamnionitis and
adverse fetal outcomes, including long-term sequelae such as cerebral palsy and chronic lung
disease (see below), standardized grading and staging of chorioamnionitis and funisitis may
facilitate study and potentially even treatment of this common condition. While many schemes
for grading and staging chorioamnionitis have been proposed, none is completely reproducible or
prospectively validated for correlation with outcomes. The scheme proposed by Redline and his
colleagues in the Society for Pediatric Pathology has good reproducibility and can serve as a start
toward standardization. In this system both the stage (localization) and grade (severity) are
determined for the maternal inflammatory response (chorioamnionitis) and the fetal
inflammatory response (chorionic vasculitis and funisitis). Maternal inflammatory response
(MIR) stage 1 represents acute subchorionitis and/or acute chorionitis in which neutrophils are
seen in the subchorionic fibrin layer or at the junction of decidua and chorion in the free
membranes. MIR stage 2 represents acute chorioamnionitis in which neutrophils extend into the
amnionic connective tissue or epithelium. MIR stage 3 represents necrotizing chorioamnionitis
characterized by karyorrhexis of neutrophils, hypereosinophilia of the amnionic basement
membrane and at least focal necrosis of the amnionic epithelium. MIR grade two is
characterized by chorionic microabscesses composed of 10 to 20 neutrophils; less inflammation
than this represents MIR grade 1. Fetal inflammatory response (FIR) stage 1 represents
inflammation around the large vessels of the chorionic plate (chorionic vasculitis) or the
umbilical vein. FIR stage 2 represents umbilical arteritis with or without chorionic vasculitis or
umbilical vein inflammation and FIR stage 3 represents necrotizing funisitis. Grade 2 is severe
inflammation and inflammation less than this is grade 1.

Clinical Consequences of Acute Chorioamnionitis and the Fetal Inflammatory Response
Syndrome

The pathogenesis of acute chorioamnionitis is likely different in term and preterm
gestations. In term gestations there is a strong relationship between the presence of ruptured
membranes and the duration of membrane rupture, and the likelihood of developing acute
chorioamnionitis. In contrast, in many preterm gestations, it appears that chorioamnionitis
precedes and, in fact causes premature membrane rupture and frequently preterm labor. In this
situation, low virulence organisms such as Ureaplasma and Mycoplasma ascend into uterine
tissues, perhaps very early in pregnancy, and eventually extend from decidua to chorion to
amnion and eventually into the amniotic fluid. Uterine contractions can be induced by
inflammatory cytokines such as IL-1, IL-6 and tumor necrosis factor produced as a result of the
inflammatory response. The inflammatory response also releases other factors such as
metalloproteases that degrade the extracellular matrix of the membranes and remodel cervical
collagen leading to premature cervical ripening and membrane rupture.
In the past, it was thought that the adverse outcomes experienced by many infants with acute chorioamnionitis were largely the result of the associated preterm labor, preterm delivery and prematurity. We have now come to understand that acute chorioamnionitis leads to a fetal reaction pattern known as the fetal inflammatory response syndrome (FIRS) and that this reaction pattern is important in the pathogenesis of many of the adverse outcomes these infants experience.\textsuperscript{16} The FIRS is defined by systemic inflammation and elevated levels of fetal inflammatory cytokine IL-6.\textsuperscript{17} FIRS correlates with a variety of adverse clinical outcomes including respiratory distress syndrome, neonatal sepsis, pneumonia, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia and necrotizing enterocolitis.\textsuperscript{16} The morphologic correlates of this fetal systemic inflammatory response are funisitis and chorionic vasculitis. Inflammation of the umbilical artery is better correlated with elevated IL-6 levels and adverse outcomes than inflammation of the umbilical vein.\textsuperscript{18, 19} Fetal vascular inflammation with associated thrombosis is even more strongly correlated with poor prognosis.\textsuperscript{20}

One of the most devastating long term complications associated with chorioamnionitis is cerebral palsy. Eastman and DeLeon noted in 1955 that infants born to mothers with fever have a seven-fold increased risk of cerebral palsy.\textsuperscript{21} Others have noted a relationship between histologic acute chorioamnionitis and cerebral palsy, particularly among preterm low and very low birth weight infants.\textsuperscript{22-25} There is experimental evidence linking infection to white matter lesions.\textsuperscript{26} Evidence that the FIRS is involved include the relationship between increased amnionic fluid cytokines and fetal plasma cytokines with intraventricular hemorrhage, white matter damage and cerebral palsy.\textsuperscript{25, 27} The morphologic correlates of the FIRS, acute funisitis and chorionic vasculitis, are also associated with increased risk of intraventricular hemorrhage, white matter damage and cerebral palsy.\textsuperscript{28-30} In fact, funisitis has been found to be a more specific predictor of poor neurologic outcomes in newborns than IL-6 levels in cord venous blood.\textsuperscript{31}

Leviton proposed several mechanisms by which inflammatory cytokines released during intrauterine infection might cause damage to the developing brain in the form of periventricular leukomalacia. These include: 1). fetal hypotension leading to brain ischemia 2). Stimulation of tissue factor production and release which may activate hemostasis resulting in coagulation necrosis of white matter 3). Release of platelet activating factor which acts as a membrane detergent to directly damage brain tissue and 4). TNF\alpha directly damages oligodendrocytes and disrupts myelinization.\textsuperscript{32} Others have noted that cytokines increase the permeability of the blood brain barrier allowing microbial products and cytokines themselves into the brain.\textsuperscript{35} Certain cytokines such as IL1 and TNF\alpha activate astrocytic populations which further disrupts the programmed sequence of normal development.\textsuperscript{33} An individual’s response may be modified by various factors. For example genetic polymorphisms in the inflammatory cytokine genes appear to increase the risk for cerebral palsy.\textsuperscript{34-36} An equivalent cytokine response may have very different effects in preterm infants compared to term infants.

The FIRS has also been implicated in the development of bronchopulmonary dysplasia (BPD).\textsuperscript{37} Several lines of evidence support the relationship between this form of severe chronic lung disease and the FIRS, which though more common in premature infants, is not explained by prematurity and treatment of respiratory distress alone. Very low birthweight infants who develop BPD have an increased incidence of chorioamnionitis but less respiratory distress.\textsuperscript{37} The risk of BPD is increased with antenatal exposure to inflammatory cytokines.\textsuperscript{38} Those preterm infants with intact membranes who had the highest IL-6, IL-8, and IL1b levels were at the greatest risk of developing BPD even when controlled for gestational age.\textsuperscript{38, 39} In animal models, these inflammatory cytokines disrupt lung development by a variety of mechanisms including
apoptosis of lung cells, decreased proliferation of certain lung cell populations, inhibition of microvascular development, and decreased expression of numerous growth. Administration of an antagonist to IL-1 prior to endotoxin administration prevents many of these changes.

**Hematogenous Infection**

Infectious agents may reach the placenta by hematogenous spread from the mother. Usually organisms that infect the placenta in this way are viruses (TORCH infections) but this pattern of spread may be seen with some bacterial infections, such as *Listeria* and syphilis and parasitic infections such as toxoplasmosis. The morphologic manifestation of infections that reach the placenta by the hematogenous route is typically villitis, or inflammation of the villi.

**Gross Features**

Villitis is usually not appreciated on gross examination of the placenta. Occasionally, small foci of necrosis may be seen. Sometimes placentas with villitis are enlarged and pale (syphilis and toxoplasmosis). In some infections, particularly *Listeria*, abscesses may be apparent on gross examination.

**Microscopic features**

Microscopically, the hallmark of a hematogenous infection is an inflammatory infiltrate in the villi. The inflammatory cells may be lymphocytes, histiocytes, plasma cells and, occasionally, neutrophils or a mixture of these. Rarely, villitis may be composed of granulomatous inflammation. Despite their location within the villi, studies have shown that the lymphocytic inflammatory cells are predominantly of maternal origin. There is often associated necrosis of the villous trophoblast and prominent villous agglutination with eosinophilic fibrinoid material; however, in some cases the inflammatory cells infiltrate the villi without destruction. Sometimes the majority of the inflammation is present around the villi (intervillositis). In addition to inflammation, the involved villi may show vascular destruction, stromal hemosiderin and fibrosis. Usually when the etiology is infectious, areas of active inflammation, resolving villitis and healed villitis with prominent fibrosis are scattered in a patchy distribution throughout the placenta. Often cases with an infectious etiology have associated chorioamnionitis. Sometimes the villitis is localized to a particular area such as stem villi or basal plate. This distribution does not appear to be related to the etiology.

**Clinical Significance**

The consequences of a hematogenous infection can be devastating and include such outcomes as stillbirth, mental retardation, learning disabilities, blindness and deafness. Therefore, it is very important for pathologists to have a high index of suspicion for infection. The morphologic features of some of the well known infectious agents can sometimes point to a particular infectious etiology that may be confirmed with immunohistochemistry, PCR, infant and maternal serologies, or even a detailed clinical history. It is important to keep in mind, however, that in the vast majority of cases of villitis (>95%) an infectious agent will not be identified on histologic sections, culture or ancillary techniques. These cases represent villitis of unknown etiology or VUE (see below). While a detailed discussion of the pathology of all the various infectious agents that may infect the placenta and fetus is beyond the scope of this discussion, I would like to examine the features of the most common infectious agent in the US to infect the infant by the hematogenous route: cytomegalovirus.
Cytomegalovirus (CMV)

Gross and microscopic features

The placenta may be normal, small, if the fetus is growth restricted, or enlarged and pale, if the fetus is anemic. The characteristic microscopic features of CMV villitis are lymphoplasmacytic inflammatory infiltrates, stromal hemosiderin, necrotizing vasculitis, occluded villous vessels and villous necrosis. In about 20% of cases the characteristic eosinophilic intranuclear and basophilic cytoplasmic inclusions can be identified in stromal, endothelial, Hofbauer or trophoblast cells. Immunohistochemistry, in situ hybridization and PCR will detect CMV in the placenta of cases of congenital CMV infection even in cases that are normal histologically or in which the infection is. In a study of 94 term placentas sent for examination for reasons other than infection, that were normal histologically, 11.7% had CMV detected by PCR: 90% of these were also positive by in situ hybridization. By in situ hybridization, CMV DNA localizes to the cytotrophoblast, syncytiotrophoblast, fetal capillaries and villous stromal cells.

Clinical features

CMV usually infects the fetus in utero. This may occur as a result of a primary maternal infection during pregnancy, the pattern typically seen in women of higher socioeconomic status, or after reactivation of latent viral infection, the pattern typical in women of lower socioeconomic status. Usually infected women are asymptomatic. Primary maternal infection is more likely to infect the fetus and these fetuses are more likely to be symptomatic. There is evidence that decidual cells or decidual macrophages may serve as a reservoir for CMV and that reactivation from these cells is enhanced as a result of the inflammatory response to concomitant bacterial infections.

In the United States, CMV is the most commonly identified infectious agent in cases of villitis where an etiology is identified. About 1% of infants are born with congenital CMV infection. About 5% to10% of these will have disseminated disease with hepatosplenomegaly, jaundice, petechiae or death. Ninety percent of congenitally infected infants will have clinically unrecognized disease and about 5% to15% of these will have long-term sequelae such as mental retardation, learning disabilities and sensorineural hearing loss. These figures indicate that congenital CMV infection represents an important public health problem. It is estimated that nearly two billion dollars is spent annually in the U.S. on the care of symptomatic infants with congenital CMV infection.

Treatment of congenitally infected infants shortly after birth may decrease the severity of neurologic damage and improve long-term outcome, therefore it is important for pathologists to have a high level of suspicion for CMV and convey positive results immediately to the pediatrician caring for these infants. There are no guidelines for treating CMV that occurs in pregnancy, making the role of screening women for CMV infection unclear.

Villitis of Unknown Etiology (VUE)

The vast majority of cases of villitis represent villitis of unknown etiology (VUE) in which an infectious etiology cannot be established. VUE will be seen in about 5% to 15% of third trimester placentas. Nearly all cases occur after 32 weeks and 80% occur after 37 weeks therefore villitis earlier than 32 weeks is more likely to have an infectious etiology.

Gross and microscopic features
Placentas from most cases of VUE are normal on gross examination. Studies have shown that the detection rate peaks at four blocks of tissue and that about 90% of cases are found with sampling of two to three blocks. Villitis can be graded based on the amount of placental parenchyma affected or on the number of villi involved per focus. Redline has proposed a scheme in which the term low grade is applied to cases in which 10 or fewer villi are involved per focus and high grade to cases with greater than 10 involved villi per focus. Focal describes those cases with only one slide involved and multifocal those with more than one slide involved. High grade cases can be separated into those that are patchy with less than 5% of all distal villi involved and diffuse with more than 5% involvement. The vast majority of cases of VUE are focal. In most cases the villitis is randomly distributed throughout the placenta but about 20% have an exclusive or partial basal/parabasal distribution, often with associated decidual inflammation. Most cases are necrotizing and the inflammatory cells are lymphocytes and histiocytes. Plasma cells are not seen in VUE and their presence should suggest CMV or other infectious etiologies. VUE may be associated with vasculitis of fetal stem vessels with downstream avascular terminal villi.

Pathogenesis

There are two schools of thought about the pathogenesis of VUE. One proposes that VUE is the result of an as yet unidentified infectious pathogen. Against this theory are the lack of symptoms in patients, the lack of seasonal variation, and failure to identify a consistent pattern of infection despite diligent searching with increasingly sophisticated techniques for several decades. Another theory proposes that VUE is an immunologic phenomenon. This seems more likely. The cells in foci of villitis have been demonstrated to be primarily maternal in origin and to represent T cells with a CD4/CD8 ratio of in the range of 0.1 to 0.5, and macrophages that exhibit up regulation of class II major histocompatibility complex antigens. The findings suggest a delayed hypersensitivity type or T-helper-1-type response as would be expected in an allograft reaction, in this case host versus graft, between maternal and fetal tissues. This theory is also in keeping with clinical features such as an increased incidence of maternal autoimmunity in women with placental VUE and the tendency for VUE to recur in some patients in subsequent pregnancies. The target antigen of maternal attack is still not known.

Clinical significance

Most cases of VUE are focal and the fetus is unaffected. When diffuse, VUE has been significantly associated with intrauterine growth restriction, oligohydramnios and chronic monitoring abnormalities including abnormal non stress tests, abnormal pulsed flow Doppler studies and abnormal biophysical profiles, diffuse perivillous fibrin deposition, and perinatal mortality. The more extensive and severe the villitis, the more likely that it will be associated with adverse outcomes.

Circulatory Disorders

Circulatory disorders of the placenta are common and are frequently clinically important for both the mother and the baby. It is important to keep in mind that the placenta has a dual circulation. Maternal blood enters the intervillous space surrounding the villi through the uterine spiral arteries. The blood percolating through this intervillous space provides nutrients to the fetus. Deoxygenated fetal blood enters the placenta through the umbilical arteries which branch over the chorionic plate and continue branching into the villous tree, ending in a capillary network in the terminal villi. After nutrient exchange, oxygen-rich blood climbs up the villous
tree and is taken to the fetus via the umbilical vein. Disorders of the maternal circulation give rise to one set of abnormalities and clinical problems while disorders of the fetal circulation give rise to another.

Infarct

Gross Features

Infarcts are common lesions seen in about 10% to 25% of placentas from normal term pregnancies. Infarcts can vary in size and shape but are usually somewhat triangular with the broad edge abutting the basal plate. They are commonly found in the peripheral regions of the placenta. All infarcts are firmer than the surrounding placental tissue and are typically very well circumscribed. Recent infarcts are dark red, firm and granular. With age they become yellow and eventually white. Occasionally, central hemorrhage with cavitation is seen.

Microscopic Features

In early infarction the villi are crowded together with narrowing or loss of the intervillous space. The fetal vessels in the affected area are dilated and congested. The syncytiotrophoblast nuclei show signs of degeneration such as nuclear pyknosis and karyorrhexis. With time, the villous stroma and syncytiotrophoblast degenerate and eventually only "ghosts" of villi remain. The intervillous space no longer contains maternal red cells. Neutrophils and macrophages may be seen at the periphery of a longstanding infarct but no true organization occurs, as occurs in infarcts in other organs.

Differential Diagnosis

On gross examination, the differential diagnosis for infarcts includes perivillous fibrin deposition and intervillous thrombohematoma. Perivillous fibrin is firm and yellow or white, like an older infarct, but it is usually not as well circumscribed and often has areas of red villous tissue interspersed with the white fibrin. Microscopically, there is expansion of the intervillous space and proliferation of trophoblast within the fibrin. Intervillous thrombohematomas are well circumscribed and firm like infarcts but they have a smooth, not granular cut surface, and are usually laminated, since they contain only blood and fibrin and lack villous tissue.

Pathogenesis

Like infarcts elsewhere in the body, placental infarcts are caused by an interruption of the blood supply to a portion of the placenta. It is maternal blood, percolating in the intervillous space that supplies and nourishes the placenta. When this blood supply is cut off, the relatively well circumscribed area of villous tissue supplied by a particular maternal vessel or group of vessels undergoes infarction. This can occur because of vascular narrowing or occlusion of the vessel as in atherosis (preeclampsia), with or without superimposed acute thrombosis, or because the supplying maternal vessel is physically separated from the placenta, as in retroplacental hematoma (placental abruption). Histologic sections of the decidua beneath an infarct may demonstrate these pathologic changes. Often the decidua is extensively necrotic indicating that the involved vessel is deep, near the myometrial-decidual junction. McDermott and Gillian have presented evidence that infarcts are also accompanied by a concomitant reduction in fetal blood flow to the villi in the infarcted area, manifesting as increased mineralization of the trophoblast membrane.
Clinical Significance
Extensive infarction, large infarcts (>3 cm), infarcts involving the central area of the placenta, and infarcts in the first and second trimester are thought to be associated with significant underlying maternal disease and interruption in the normal uteroplacental blood flow.\cite{58,60} Preeclampsia represents a major risk factor for infarction. There is a strong relationship between the severity of preeclampsia and the extent of infarction.\cite{61} Increased rates of placental infarction have also been reported in a variety of thrombophilic conditions including factor V Leiden mutation heterozygosity, prothrombin gene variants, hyperhomocysteinemia, and antiphospholipid antibodies.\cite{62-65}

Extensive infarction may have serious consequences for the fetus including intrauterine fetal demise, hypoxia, and intrauterine growth retardation both at term and in preterm infants.\cite{66-67} It is thought that the normal placenta can withstand the loss of as much as 15 to 20% of the villous tissue without adversely affecting the fetus, but in conditions in which there is already poor uteroplacental perfusion, such as preeclampsia, even lesser degrees of infarction may be detrimental to the fetus. Lesions which cause a disturbance of uteroplacental circulation, including extensive infarction, in the placentas of preterm infants has been significantly associated with periventricular leukomalacia.\cite{68} High rates of infarction and low flow changes were also noted in a series of stillborn infants with ischemic cerebral injury.\cite{69} However, this association has not been found by all.\cite{70}

Massive Perivillous Fibrin Deposition
Some fibrin is seen normally in most placentas and is particularly common beneath the chorionic plate, around stem villi, and above the basal plate. This type of fibrin deposition is thought to be due to local stasis and eddy currents in these areas and may actually reflect good intraplacental blood flow, as this type of fibrin deposition is seen less commonly in placentas from abnormal pregnancies such as those complicated by preterm delivery and diabetes.\cite{71}

Gross Features
Large amounts of fibrinoid material can be appreciated grossly as firm white, yellow or brown plaques. These may be slightly granular or smooth. Often they are located in the periphery of the placenta where they fill in the angle where the fetal membranes meet the basal plate. Much less commonly the fibrinoid material forms thick white or grey strands that replace much of the placental parenchyma leaving only small pockets of interspersed red villous tissue.

Microscopic Features
Microscopically, the terminal villi are widely separated and enmeshed in an abundant amount of eosinophilic fibrinoid material that obliterates the intervillous space. In early lesions, the syncytiotrophoblast shows signs of degeneration and eventually disappears leaving behind a thickened trophoblastic basement membrane. The trophoblast show a marked degree of proliferation and extends out into the perivillous fibrin in clusters. The villous stroma becomes progressively more fibrotic and eventually there is obliteration of fetal vessels.

In order to separate the normal amount of fibrin seen in the placenta from fibrin deposition that is likely to be clinically significant, Katzman and Genest have proposed some quantitative definitions.\cite{72} They define transmural massive perivillous fibrin deposition (MFD) as perivillous fibrinoid material that extends from the maternal to the fetal surface encasing greater than or equal to 50% of the villi on at least one slide.\cite{72} Borderline MFD is transmural or nearly transmural and encases 25% to 50% of the villi on at least one slide.\cite{72}
**Differential Diagnosis**

The differential diagnostic considerations include maternal floor infarct, placental infarct, fibrin associated with chronic villitis and fibrinoid deposition after fetal death with retained placenta. Maternal floor infarct overlaps significantly with massive perivillous fibrin deposition and these entities are likely part of the same spectrum. Maternal floor infarct has similar microscopic features, shares similar clinical features and often is associated with massive perivillous fibrin deposition. By definition, maternal floor infarct involves the villi, and often the decidua, near the maternal surface and should involve a large amount of the maternal floor. Infarcts may be difficult to distinguish from perivillous fibrin deposition grossly as both may be yellow or white and firm. Infarcts tend to be more sharply circumscribed and about the maternal surface of the placenta. Microscopically, infarcts show collapse rather than expansion of the intervillous space, no trophoblast hyperplasia, and necrosis rather than fibrosis of the villous stroma. Fibrin deposition associated with chronic villitis can be distinguished from massive perivillous fibrin deposition because it usually has associated areas of active villitis. The clinical history of intrauterine fetal demise will point to the correct diagnosis of villous fibrosis on this basis. This is usually diffuse.

**Clinical Features**

Extensive perivillous fibrin deposition, while quite rare, involving less than 1% of examined placentas, is an important lesion for pathologists to recognize because it is associated with a high rate of adverse fetal outcome. What is likely to be clinically significant is the location of the perivillous fibrin and the number of villi that are ischemic as a result of it. Redline and Patterson observed that perivillous fibrin that entrapped more than 20% of the terminal villi in the central basal portion of the placenta, which is thought to be the major nutrient-exchanging region of the placenta, was significantly associated with intrauterine fetal growth retardation and low placental weight. Although not as carefully localized or quantitated, a study by Fuke et al also found a significant relationship between massive perivillous fibrin deposition and intrauterine growth retardation. These workers observed that the combination of intrauterine growth retardation and MFD could recur in subsequent pregnancies and could be prevented with anticoagulant therapy. Katzman and Genest reported a 31% incidence of IUGR in cases with MFD. About 14% of their cases had recurrent MFD or maternal floor infarct in subsequent 2nd or 3rd trimester placentas and 50% had increased perivillous fibrin or maternal floor infarct in 1st trimester placentas. Katzman et al found a significant relationship between lesions which cause a disturbance of uteroplacental circulation, including MFD, in the placentas of preterm infants and periventricular leukomalacia.

**Retroplacental Hematoma/Placental Abruption**

**Gross Features**

A retroplacental hematoma is a blood clot that lies between the basal plate of the placenta and the uterine wall and indents the overlying placental parenchyma. It may be large, covering most of the maternal surface, or small, best visualized on serial sections. A recent retroplacental hematoma will be soft and red and will easily separate from the placenta. An indentation, a disrupted maternal surface, a large amount of clot in the specimen container, the delivering physician's impression of the placenta when delivered or at the time of Cesarean section may all point to the diagnosis in the absence of adherent clot on the placenta. Older hematomas are firm, brown and adherent. Sometimes the placental parenchyma overlying retroplacental hematomas is infarcted, particularly if the hematoma is not very recent. Occasionally a hematoma may rupture
and dissect into adjacent villous tissue. In a very recent retroplacental bleed there may be no clot adherent to the placenta and no deformation of the maternal surface.

**Microscopic Features**

Early hematomas are composed of red cells while older ones contain varying amounts of fibrin, degenerated red cells, hemosiderin-laden macrophages and neutrophils. The overlying decidua may be necrotic. Villous stromal hemorrhage and villous edema may be seen adjacent to retroplacental hematoma, particularly when the hematoma occurs in the second trimester. Retroplacental hematomas, particularly large hematomas and those that are not recent, may be associated with infarction.

**Clinical Features**

Retroplacental hematomas are common, occurring in as many as 4.5% of placentas. The most consistently identified risk factors for retroplacental bleeding include preeclampsia with a three fold increased risk, abdominal trauma, cigarette smoking, both maternal and of the male partner, a previous history of abruption, extremes of maternal age, multiparity, poor nutrition, low socioeconomic status, acute chorioamnionitis, severe fetal growth retardation, maternal thrombophilic conditions, and cocaine abuse.

Retroplacental hematoma is related to, but not synonymous with, the clinical syndrome of placental abruption (abruptio placentae). The features of this clinical syndrome include vaginal bleeding, increased uterine tone, uterine tenderness, diminished fetal heart tones and if severe, maternal hypovolemia, consumptive coagulopathy, and fetal death. The incidence of abruption is about 11.5/1000 deliveries. It is associated with a 20% to 40% fetal mortality rate and accounts for 10% of all stillbirths and 6% of all maternal deaths in developed countries. The rate of placental abruption in the United States has increased in the last few decades.

Retroplacental hematoma and placental abruption share many of the same risk factors and a clear distinction between them has not always been made in the literature. There is poor concordance between the clinical and pathologic criteria for abruption/retroplacental hematoma. In only about a third of the cases with a clinical diagnosis of abruption can a retroplacental hematoma be demonstrated on placental examination, probably because of the rapidity of development and subsequent delivery. Conversely, in only about a third of cases in which the pathologist identifies a retroplacental hematoma will the clinical syndrome of placental abruption have been diagnosed. These probably represent smaller, clinically insignificant hematomas.

The clinical significance of retroplacental hematoma is largely dependant on the size and the amount of placenta that is infarcted, keeping in mind that in a background of chronic uteroplacental ischemia, such as with preeclampsia, the functional reserve of the placenta will be exceeded with lesser degrees of infarction. Gross lesions with disturbance of uteroplacental circulation, including massive retroplacental hematoma has been associated with periventricular leukomalacia in preterm infants. Extensive retroplacental hematoma with infarction may also cause fetal death.

**Pathogenesis**

The pathogenesis of retroplacental hematoma is not well understood. It is thought that in cases of preeclampsia the associated atherosis may weaken the vessels increasing the likelihood of rupture. Cigarette smoking and cocaine abuse may also damage vessels walls. Hyperhomocysteinemia and hereditary deficiencies in various factors involved in normal coagulation may also lead to repeated thrombosis and possibly vascular damage.
Fetal Thrombotic Vasculopathy

Occlusion of vessels in the fetal circulatory system can involve vessels at any level - large umbilical cord vessels, their branches on the chorionic plate, or smaller capillary fetal vessels within the chorionic villi. During gestation there is one continuous circulation between the fetus and the placenta. The term fetal vascular obstruction used in this discussion refers to thrombi, or related downstream lesions, in the fetal portion of the placental circulation. It has become increasingly clear that thrombotic lesions in the placental part of this fetal circulation may be associated with, and could serve as a marker for, thrombotic or embolic lesions in the circulation of the fetus itself, sometimes with devastating consequences for the fetus. For this reason, it is important for pathologists to become familiar with the gross and microscopic appearance of fetal vascular obstructive lesions in the placenta.

Gross and Microscopic Features

Areas of avascular terminal villi downstream from vascular obstruction in the placenta or cord form well circumscribed, pale areas with the same spongy consistency as the surrounding placental tissue. The affected villi are sharply demarcated, both grossly and microscopically, from adjacent normal villi. Microscopically, the villi are avascular and the villous stroma exhibits an increased amount of bland eosinophilic stromal hyaline fibrosis. The villi are normally spaced within the intervillous space.

Redline et al. recently proposed diagnostic terminology with precise, reproducible definitions for lesions of fetal vascular obstruction. The term uniformly avascular villi is used when three or more foci of two terminal villi show avascularity. Another form of fetal vascular obstruction that manifests in distal villi has been termed villous stromal-vascular karyorrhexis. This can be diagnosed when three or more foci of two or more terminal villi show karyorrhexis of fetal cells either endothelium, stromal cells or blood cell elements. Often the villi are hypovascular with degenerating capillaries and fragmented red cells. This lesion has been termed hemorrhagic endovasculitis in the past. It is now thought to represent part of the spectrum of changes in fetal vascular obstruction as both patterns may coexist, both share the same predisposing risk factors and both carry similar implications for the fetus. All of these villous changes are considered severe when there are more than two foci that average 15 or more villi per focus per slide. It is recommended that the term fetal thrombotic vasculopathy be reserved for those cases in which the villous vascular obstruction is this extensive. Massive thrombosis may involve 25 to 50% of the placental parenchyma.

A thrombosed large vessel upstream from avascular terminal villi or villous stromal-vascular karyorrhexis can only be demonstrated in about a third of cases when extensive avascular villi are present. The distal villous changes may be more sensitive and reproducible evidence of fetal thrombotic vasculopathy than thrombotic lesions in large vessels.

Differential Diagnosis

The differential diagnosis on gross examination is primarily with an infarct. Both an infarct and an area of avascular terminal villi will be well circumscribed and all but very recent infarcts will be pale. In contrast to areas of avascular villi which have the same spongy consistency as the surrounding placental tissue, infarcts are always more firm than surrounding tissue. Microscopically, infarcts will show crowded villi with collapse of the intervillous space, whereas the villi in fetal vascular obstruction will be normally spaced. The villi in infarcts
exhibit ischemic necrosis whereas those in fetal vascular obstruction show dense, eosinophilic stromal fibrosis.

Another differential diagnostic consideration, especially on microscopic examination, is with the villous changes associated with intrauterine fetal demise. The microscopic changes may be very similar to fetal vascular obstruction, but with intrauterine fetal demise, the process is generalized involving all villi and all vessels of a similar size to the same degree, in contrast to the sharply demarcated areas of avascularity in fetal vascular obstruction.

A third process in the differential diagnosis is villitis of unknown etiology with stem villitis and avascular villi. In this condition, the placenta will show areas of active and healed villitis with villitis involving the stem villi, including the vessels which show obliteration and downstream avascular villi. This diagnosis should only be made in the setting of active villitis.

Pathogenesis

Thrombotic vascular obstruction in the fetal circulation may have several mechanisms, including a hypercoagulable state, vascular damage and stasis. Fetal coagulation factor abnormalities or hereditary thrombophilias in the fetus alone probably explain very few of these cases but may provide a substrate that when combined with other factors can tip the balance towards thrombosis. There is an association between fetal thrombotic vasculopathy and a variety of cord abnormalities including velamentous cord insertion, excessive cord twisting, nuchal cord, other encirclements, and very long cords. These cord abnormalities promote vascular stasis and the development of clot which may be propagated with downstream effects or embolize downstream or into the circulation of the fetus itself. There is also an association between fetal vascular obstruction and chorioamnionitis. The mediators of the inflammatory process trigger the coagulation cascade at several points. The incidence of thrombosis in the placental part of the fetal circulation is also increased in the placentas of diabetic mothers for reasons that are not well understood.

Clinical Features

Very extensive avascular villi, involving 40 to 60% of the placental tissue, may cause sudden intrauterine or intrapartum fetal death due to massive placental dysfunction. Fetal thrombotic vasculopathy as defined above, is associated with cerebral palsy, perinatal liver disease, fetal and neonatal thromboembolic disease and discordant growth in twins.

Fetal vascular obstructive lesions in fetal circulation of the placenta may be associated with thrombotic lesions in the fetus itself or with fetal conditions such as cerebral palsy that may have thrombosis as part of its pathogenesis. Redline and Pappin, using avascular villi as a marker of this process, found that cases with extensive areas of avascular villi were significantly associated with fetal growth retardation, oligohydramnios in the absence of membrane rupture and acute and chronic monitoring abnormalities. In a subset of this group that was over 34 weeks, did not have malformations and did not have other major placental pathology, the presence of very large areas of avascular villi, diffuse platelet aggregates or intravascular fibrin strands was highly associated with major thrombotic events in the fetus. In a study of term, singleton infants with neonatal encephalopathy, McDonald et al found that fetal thrombotic vasculopathy, as well as funisitis and accelerated villous maturation were all independently and significantly associated with neonatal encephalopathy. Kraus has described a high rate of downstream avascular villi and thrombi in fetal placental vessels in a selected group of infants with cerebral palsy referred for the purpose of litigation. Redline et al, studying a similar population, also found extensive avascular villi in about 18% of term cases with long-term neurologic impairment. Potentially obstructing umbilical cord abnormalities were much more...
likely in infants with fetal thrombotic vasculopathy. In a study of 84 consecutive perinatal autopsies, Kraus found fetal vascular obstructive lesions in the placentas of 16 cases.\(^{94}\) The areas of fetal vascular obstructive lesions were extensive in the placentas of all cases and occupied 25 to 40% of the placenta in four cases. In these four cases, the extensive fetal vascular obstructive lesions were the only explanation for the fetal death. Six of these cases had thrombi in fetal organs including the brain, kidney and lungs. Eight of the mothers had an extensive work up for coagulopathy and five had one or more coagulation abnormalities.\(^ {94}\)

These findings indicate that fetal vascular obstructive lesions in the placenta, particularly if extensive, may be a reliable indicator of the potential for thrombi in the circulation of the fetus or newborn and may explain adverse perinatal outcomes and some perinatal deaths. It should be clear that the process of thrombosis occurs well before labor and delivery. Prospective studies will be needed to determine the predictive value of fetal vascular obstructive lesions for various adverse fetal outcomes such as neurologic impairment. Further studies are also needed to determine the clinically significant amount of avascular villi, the appropriate work up for this finding, and what role, if any, there is for treatment in subsequent pregnancies.

References:


