

The Placenta as a Fetal Organ

Jeffrey D. Goldstein, M.D.

Senior Physician and Chief of Clinical Pediatric Pathology

Department of Pathology and Laboratory Medicine

Mattel Children's Hospital and Ronald Reagan UCLA Medical Center

David Geffen School of Medicine at UCLA

With a little help from my friends:

Ona Marie Faye-Petersen, M.D., University of Alabama, Birmingham

Robert W. Bendon, M.D., Kosair Children's Hospital, Louisville

Linda M. Ernst, M.D., Northwestern University, Chicago

Yee Khong, M.D., Women's and Children's Hospital, University of Adelaide

How do you ...

- Accession Placentas?
- Identify the Baby's Physician?
- Route Routine Reports?
- Define and Communicate "Critical" Values?

Practice Guideline for Examination of the Placenta

Developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists

Claire Langston, MD; Cynthia Kaplan, MD; Trevor Macpherson, MD; Elizabeth Mancini, MD; Keith Peevy, MD; Barbara Clark, PA-C; Cathy Murtagh, PA-C; Susan Cox, MD; Guy Glenn, MD

• The Placental Pathology Practice Guideline Development Task Force, a multidisciplinary group, has prepared this guideline to assist those involved with placental examination. It provides recommendations related to indications and methods for placental examination as well as sample worksheets. An algorithm for the handling of placentas summarizes the recommendations of the guideline. A summary of specific findings of placental examination together with their pathogenesis and clinical associations is also provided. Recommendations related to reporting with sample reporting formats are included. The guideline is intended as an educational tool, and its use should be guided by the individual circumstances and care setting of specific cases.

(Arch Pathol Lab Med. 1997;121:449-476)

3. Practice guidelines should be as comprehensive and specific as possible.

4. Practice guidelines should be based on current information.

5. Practice guidelines should be widely disseminated.

Several definitions are important to the development, understanding, and use of practice guidelines.

Parameters.—Practice parameters are strategies for patient management developed to assist physicians in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies.

Standards.—Standards are accepted principles for patient management. Practice variation owing to patient- or physician-specific factors is not expected.

Indications for Placental Examination

Maternal

- › Delivery at <37 wks or more than 42 wks (alternative: <34 wks only)
- › Unexplained or recurrent pregnancy complications
- › Systemic disorders, gestational or underlying, including malignancy with concern for mother or infant
- › Peripartum fever or infection
- › Excessive third-trimester bleeding
- › Thick or prolonged meconium
- › Severe oligohydramnios/polyhydramnios

Fetal/neonatal

- › Stillbirth or neonatal death
- › NICU admission
- › SGA/LGA (birthweight <10th or >90th percentile for gestational age)
- › Birth depression/pH <7.0 / 5-minute Apgar <7/ assisted ventilation >10 min
- › Neonatal hematocrit <35
- › Neonatal seizures
- › Suspected infection or sepsis
- › Hydrops fetalis of unknown etiology
- › Multiple pregnancy (alternative: fused placentas, same-sex twins, and/or twins with discordant fetal growth)

Placental

- › Structural abnormalities or masses involving the placental disc, umbilical cord, or membranes
- › Abnormal size for gestational age
- › Fragmented, possibly incomplete placenta

Source: College of American Pathologists Practice Guideline, 1997

Society for Pediatric Pathology, Perinatal Section Nosology Committees

Redline RW, Ariel I, Baergen RN, Desa DJ, Kraus FT, Roberts DJ, Sander CM. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol*. 2004 Sep-Oct;7(5):443-52.

Redline RW, Boyd T, Campbell V, Hyde S, Kaplan C, Khong TY, Prashner HR, Waters BL;. Maternal vascular underperfusion: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol*. 2004 May-Jun;7(3):237-49.

Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C; Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol*. 2003 Sep-Oct;6(5):435-48.

Sampling and definitions of placental lesions: Amsterdam Placental Workshop Group Consensus Statement.

Khong TY, Mooney EE, Ariel I, Balmus NCM, Boyd T, Brundler MA, Derricott H, Evans M, Faye-Petersen OM, Gillan JE, Heazell AE, Heller DS, Jacques S, McKay EM, Keating S, Kelehan P, Maes A, Morgan TK, Nikkels PGJ, Parks WT, Redline RW, Scheimberg IB, Schoots MH, Sebire NJ, Timmer A, Turowski G, van der Voorn JP, van Lijnschoten I, Gordijn SJ.

Archives of Pathology and Laboratory Medicine; *in Press*

Amsterdam 2014 Placental Consensus

- To establish an agreed protocol for sampling the placenta, and for diagnostic criteria for placental lesions
- Assist international comparability of clinico-pathologic and scientific studies and assist in refining the significance of lesions associated with adverse pregnancy and later health outcomes.

Amsterdam 2014 Consensus Gross Examination Recommendations

- Trimmed Weight
- Fixation (May add 3-6%)
- Prior histologic sampling
- Disruption of the basal plate
- Reference to contemporary weight standards

Weight References

- Pinar et al: Pediatric Pathology and Laboratory Medicine 16:901-907, 1996. (Singleton & Twins)
- Pinar et al: Pediatric and Developmental Pathology 5:495, 2002 (Triplets)
- Kalousek et al: Pathology of the human embryo and previsible fetus. Springer-Verlag 1990. (Developmental ages 8-18 weeks)

(Tables reprinted in AFIP/ARP Placenta Non-Tumor Fascicle)

Amsterdam 2014 Consensus Gross Examination Recommendations

- Chorionic Disk Dimensions x 3
(maximum and minimum thickness)
- Membranes – color/opacity, completeness
Percentage involved by circumvallation or
circummargination

Distance from rupture site to disk edge –
No consensus (Previa if at edge)

Amsterdam 2014 Consensus Gross Examination Recommendations

- Umbilical Cord
 - Average diameter
 - Length
 - Insertion site – distance to nearest edge if < 3 cm
 - Strictures and knots
 - Coiling (<1 or >3 / 10 cm)
 - Segmental hypercoiling
 - Deep grooves
 - Coil direction ('handedness')

Coil direction ('handedness')



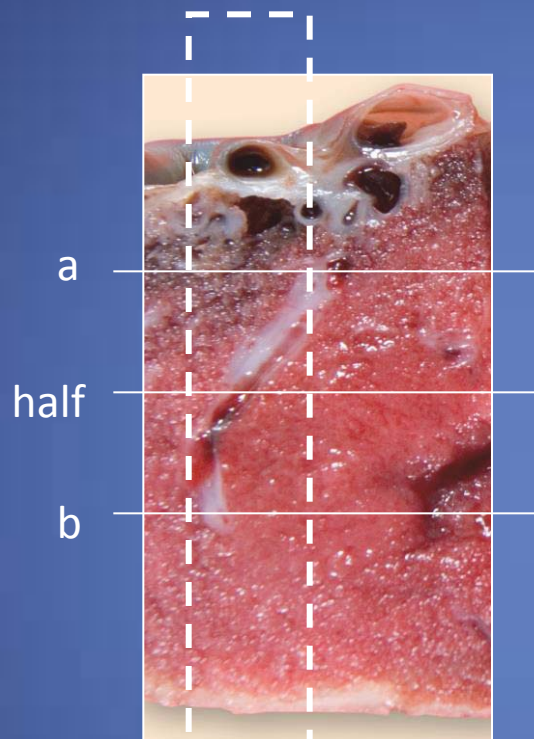
Left Hand - Counterclockwise

Ernst LM, et al. Placenta. 2013 Jul;34(7):583-8.

Coiling Pattern	Frequency	Abnormal cord insertion	Fetal thrombi	Avascular villi	Fetal thrombotic vasculopathy	Stillbirth
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Left twist	261 (81)	45 (17)	51 (20)	45 (17)	16 (6)	12 (5)
Right twist	61 (19)	9 (15)	22 (36)	18 (30)	9 (15)	7 (11)
P-value		NS	0.006	0.030	0.023	0.04

Amsterdam 2014 Consensus Gross Examination Recommendations

- Routine Histologic Sampling
 1. Membrane roll + umbilical cord: fetal end & 5 cm from insertion
 2. Full thickness close to umbilical cord insertion site
 - 3 and 4. Full thickness from central 2/3 of Disc



narrow
slice

a
upper third



b
lower third



narrow slice
upper half



narrow slice
lower half



upper half



lower half



Khong TY, et al: Arch Pathol Lab Med;
in press

Amsterdam 2014 Consensus Gross Examination Recommendations

- Lesions
 - Number and Location
 - Size (Dimensions and Estimate of Placental Volume)
 - Sample each type of lesion with adjacent normal parenchyma (up to 3 additional blocks)

Microscopically different lesions may appear similar grossly.

Amsterdam 2014 Consensus Terminology

- Maternal Vascular Malperfusion

Preferred over “Underperfusion”

Gross Features

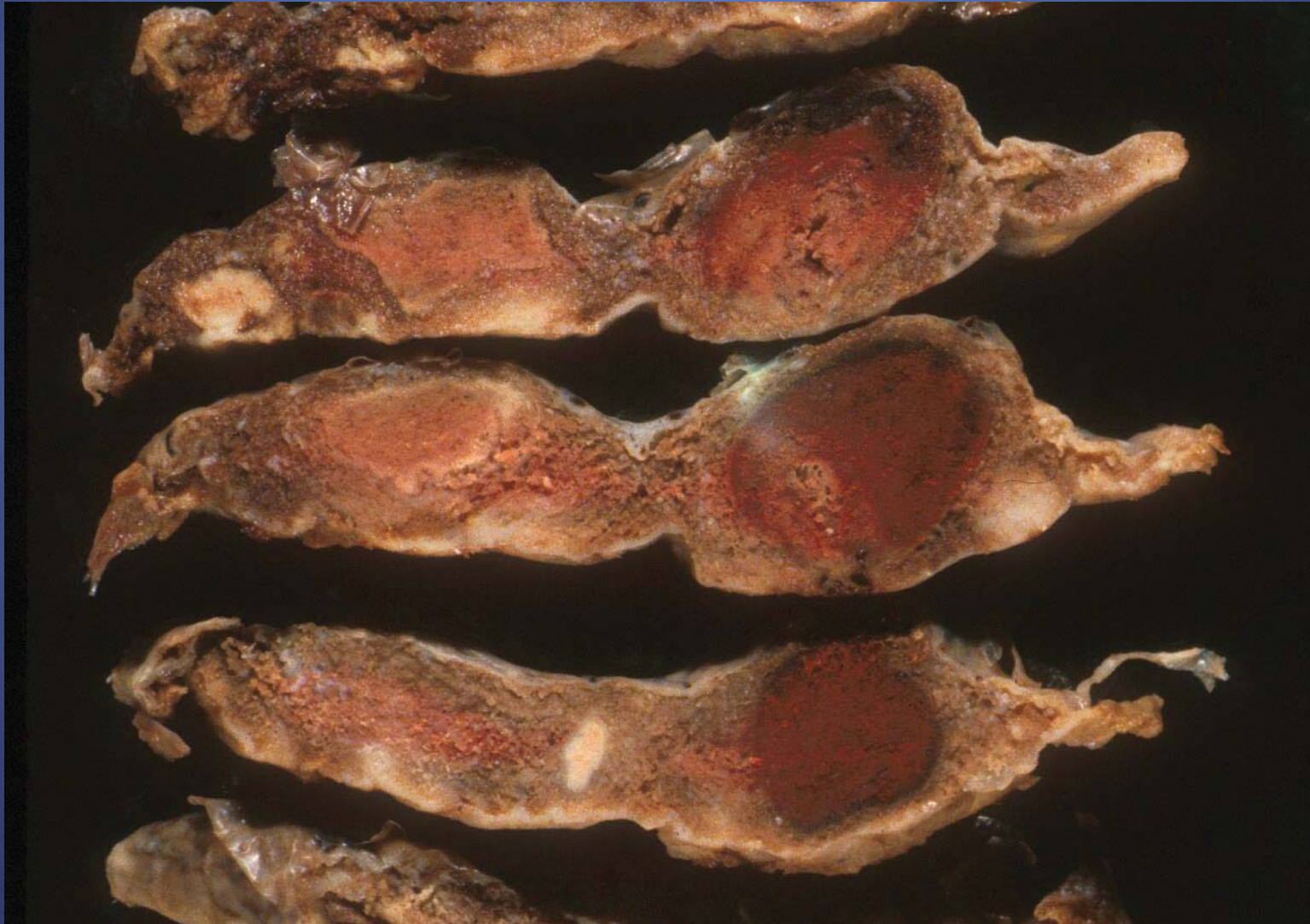
Hypoplasia (< 10th Percentile)

Thin umbilical cord (<8 mm at term or 10th Percentile)

Infarcts (Any preterm; >5% non-peripheral at term)

Retroplacental hemorrhage

Multiple Infarcts, Different Ages



Maternal Vascular Malperfusion

Microscopic Features

Distal villous hypoplasia

Accelerated villous maturation

Decidual arteriopathy

Acute atherosclerosis

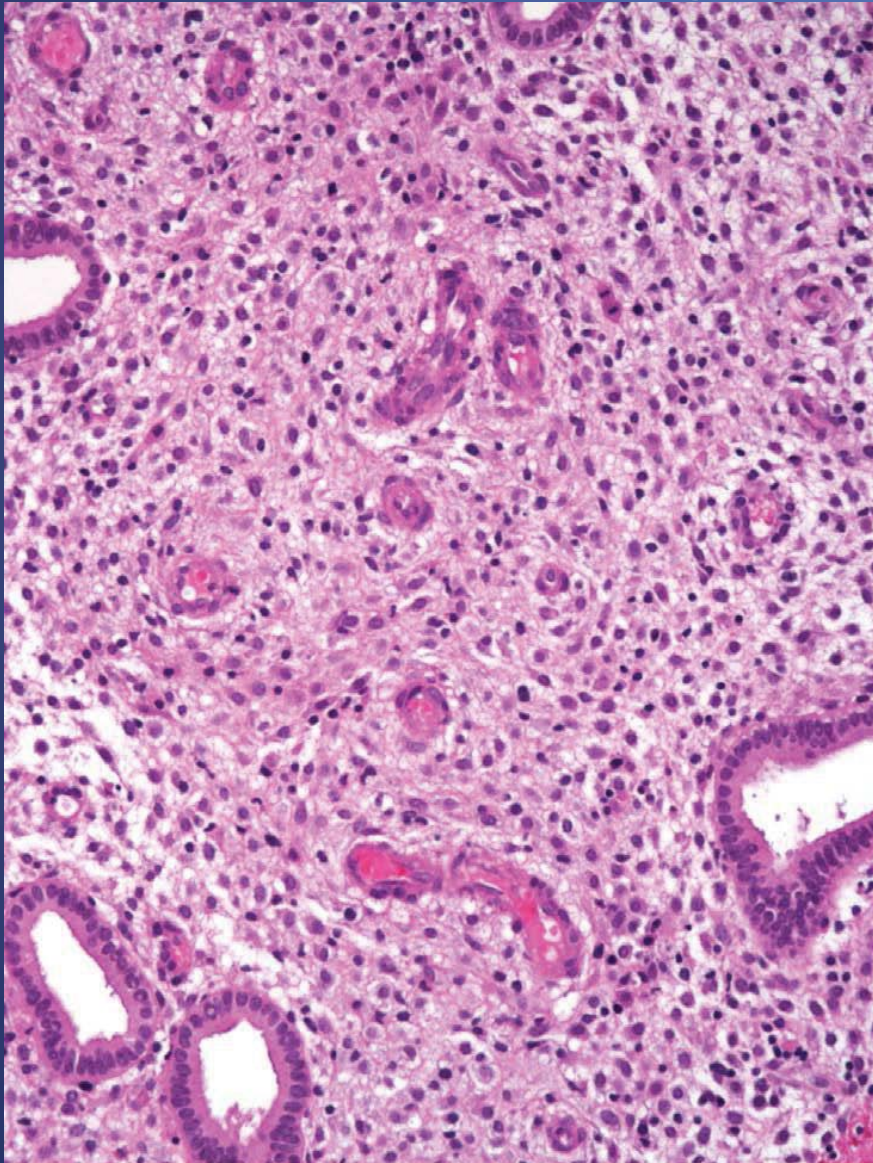
Fibrinoid necrosis or thrombosis

Absence of remodeling & mural hypertrophy

3rd trimester persistence of intramural trophoblast

Normal Endometrial Spiral Arteries

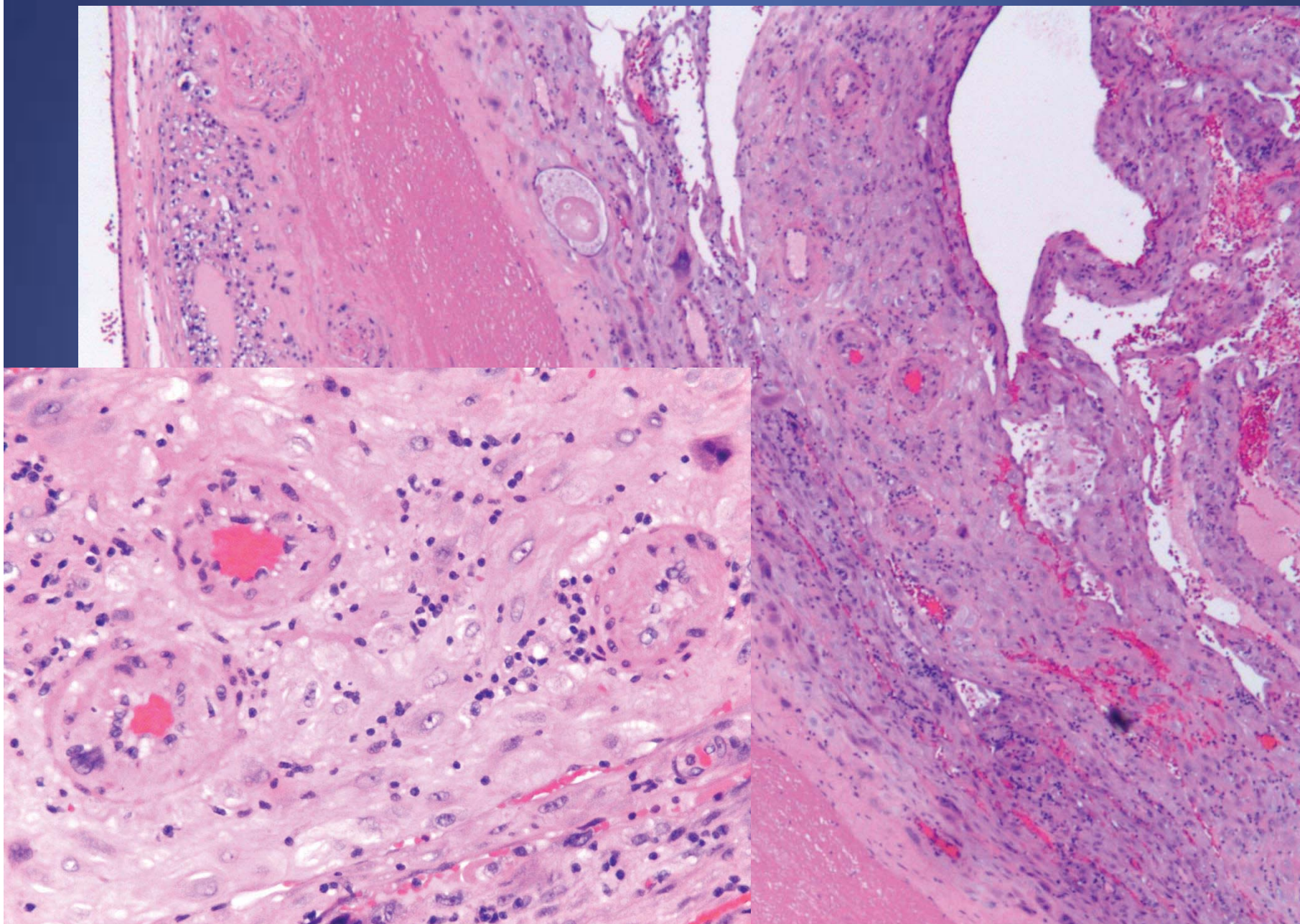
Before Remodeling



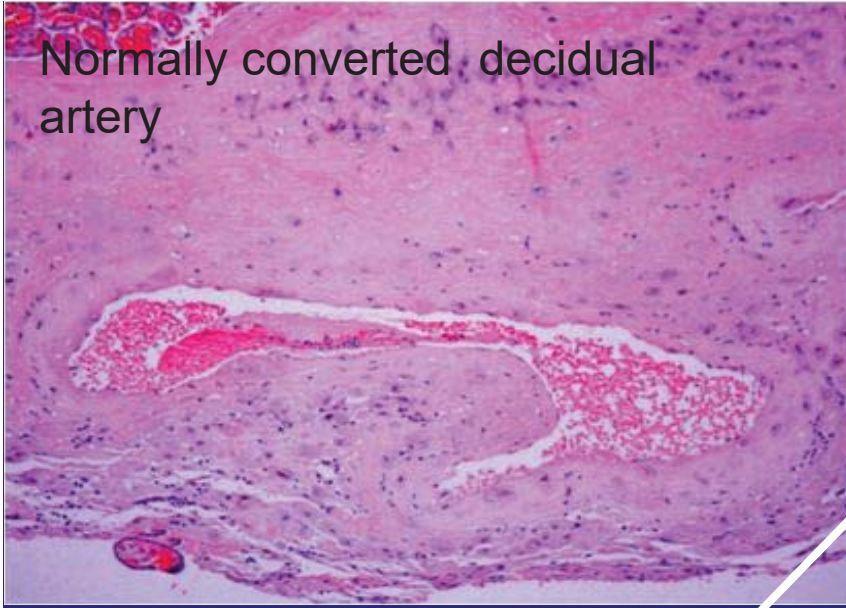
After Remodeling



Failure of Remodeling of Spiral Arteries

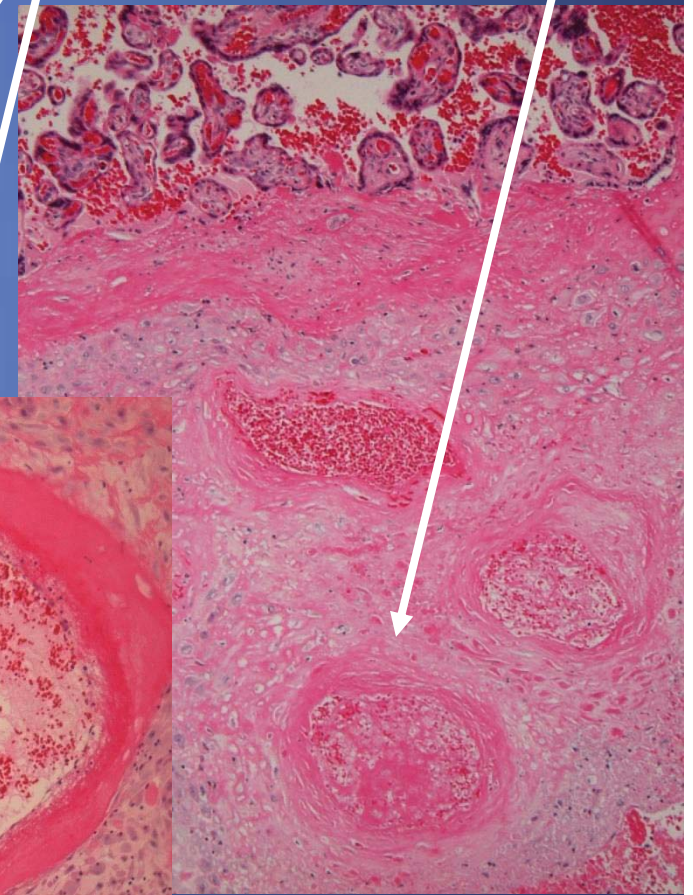
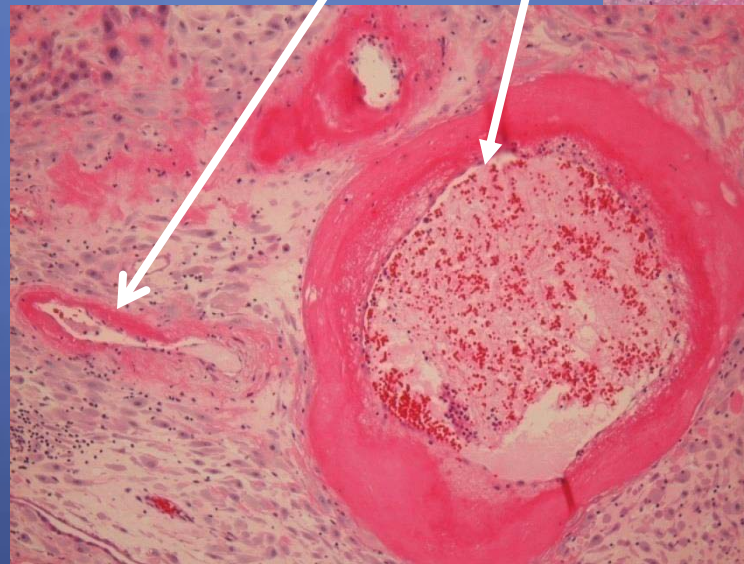
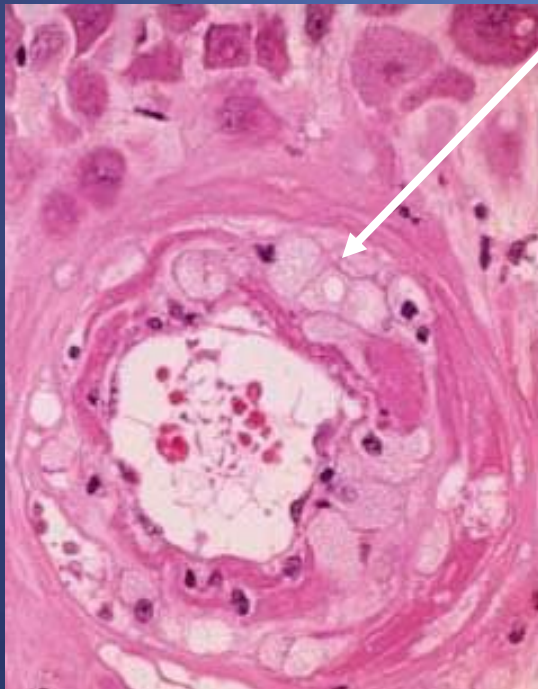


Normally converted decidual artery



Decidual arteriopathy with narrowing classic for but not limited to preeclampsia

Atherosclerosis, fibrinoid necrosis, and thrombosis

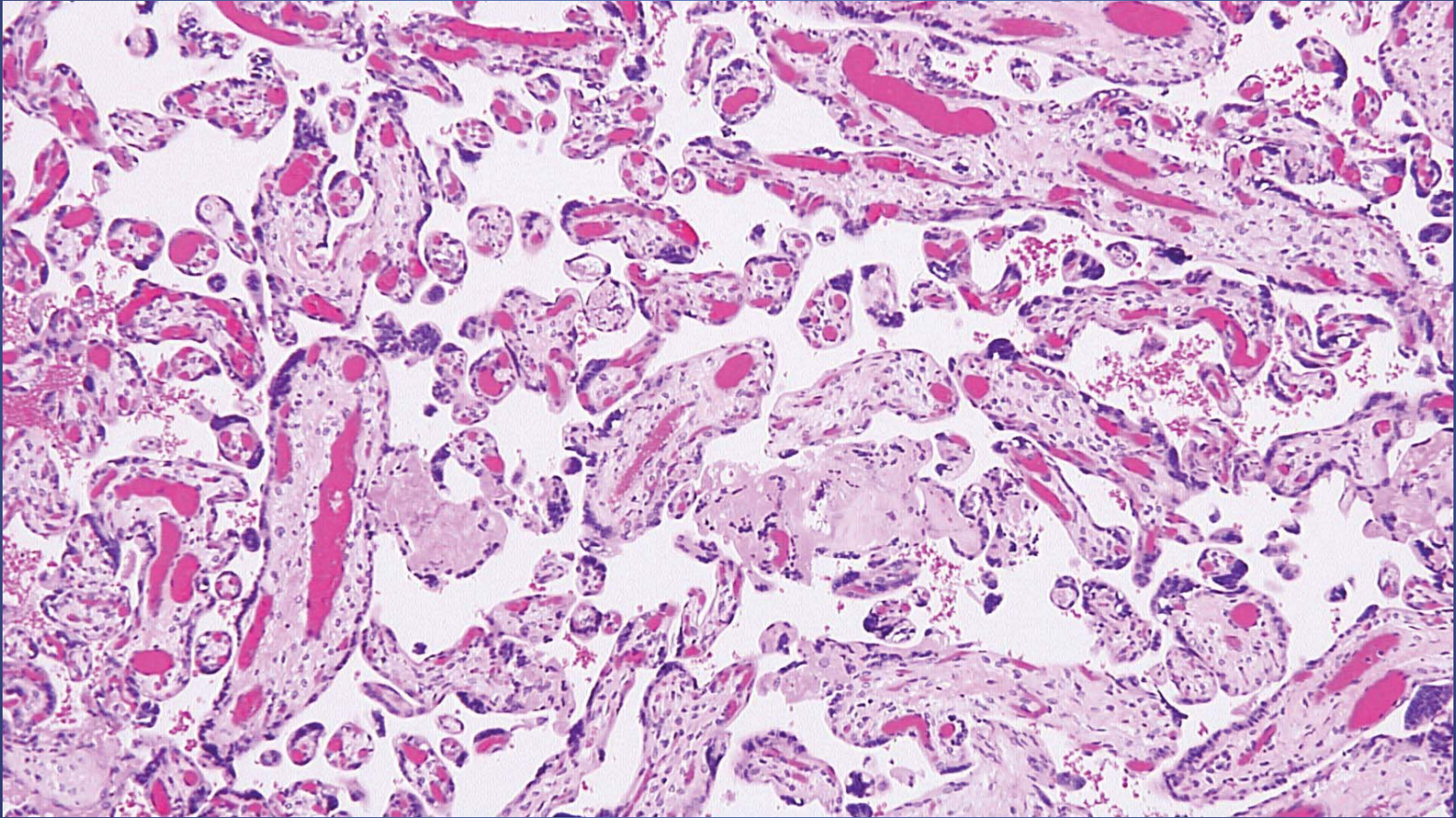


Distal Villous Hypoplasia

Usually <32 Weeks Gestation

Widened Intervillous Space with Paucity of Terminal Villi Relative to Stem Villi

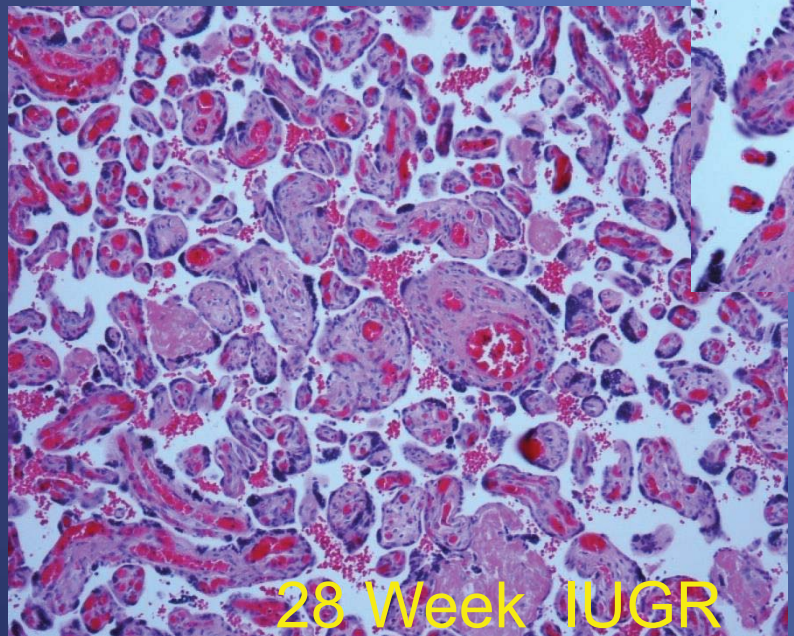
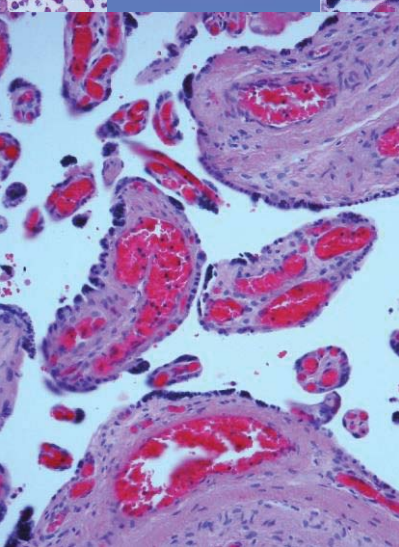
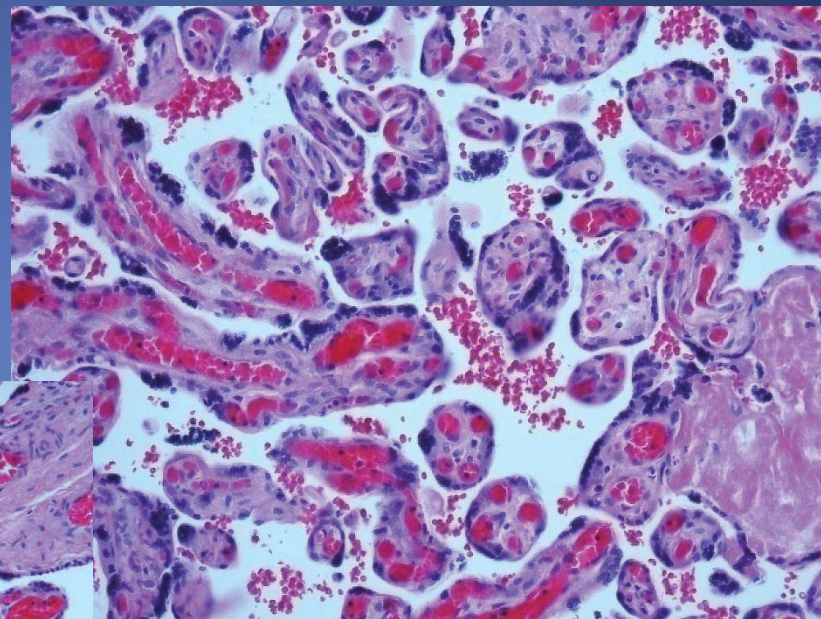
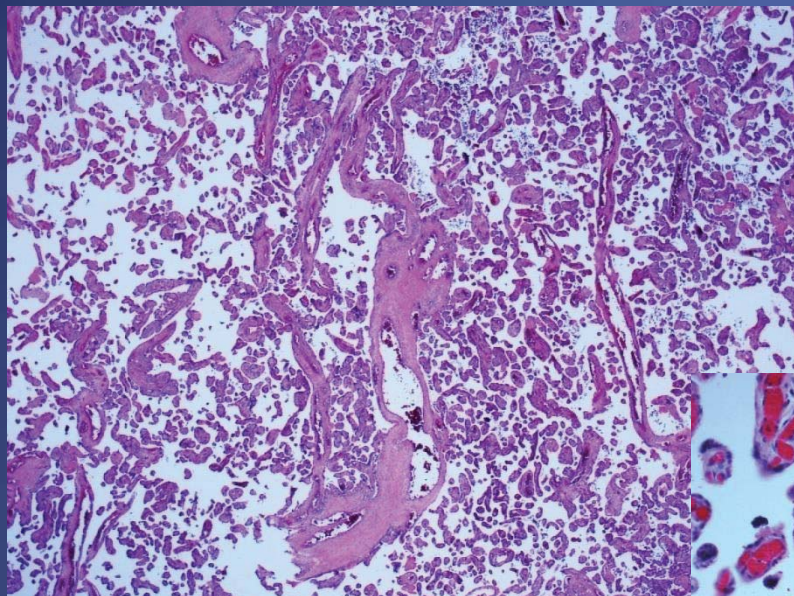
Thin Elongated Terminal Villi



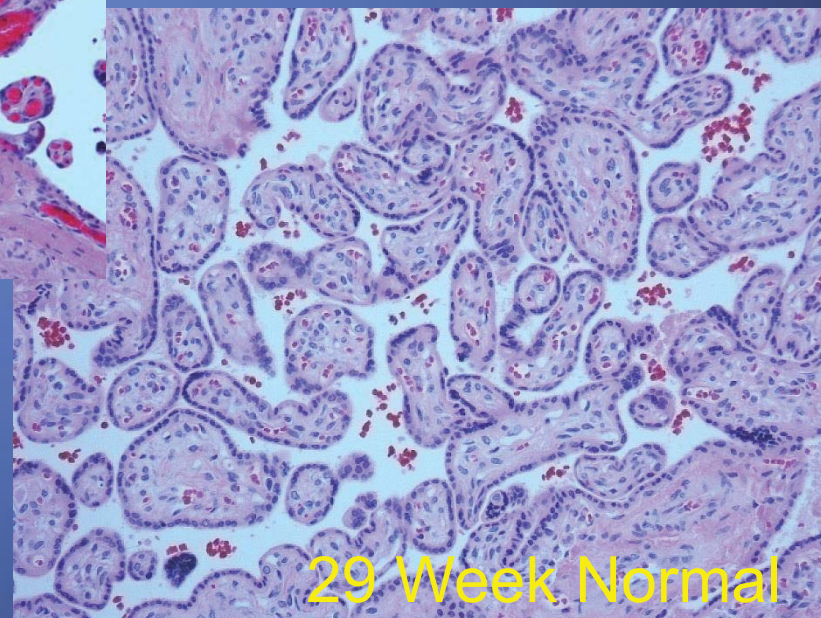
Lower 2/3 Chorionic Plate
30% full thickness slide

Focal = 1 slide
Diffuse \geq 2 slides

Accelerated Villous Maturation (NB 28 Wk GA IUGR)



28 Week IUGR



29 Week Normal

Maternal Vascular Malperfusion

Insufficient Evidence / Inconclusive

Chorionic pseudocysts

≥ 3 microscopic chorionic lakes per section of a membrane roll or grossly unremarkable placental parenchyma

Membranous (Laminar) Decidual Necrosis

A band of coagulative necrosis of choriondecidual interface of placental membranes (at least 10% of membrane roll)

Increased Extravillous trophoblast (“X-cell”) Islands

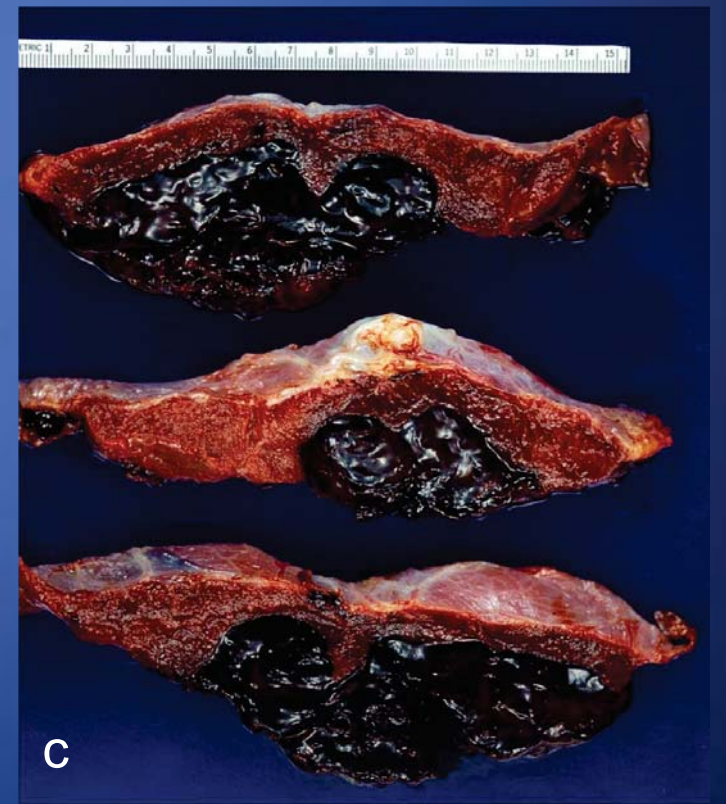
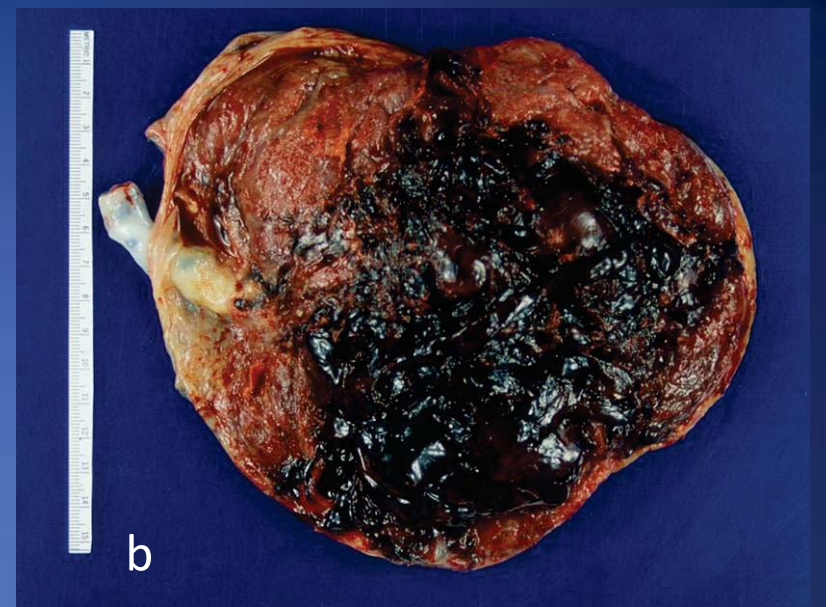
≥ 5 cell islands and/or placental septa with ≥ 50 extravillous trophoblastic cells per placental section or membrane migratory trophoblastic layer > 7 cells thick

Acute Retroplacental Hematoma



Loosely adherent clot (a)

Early organizing, adherent clot (b)
with compression of maternal
surface (c)



c

Retroplacental Hemorrhage

Microscopic Features

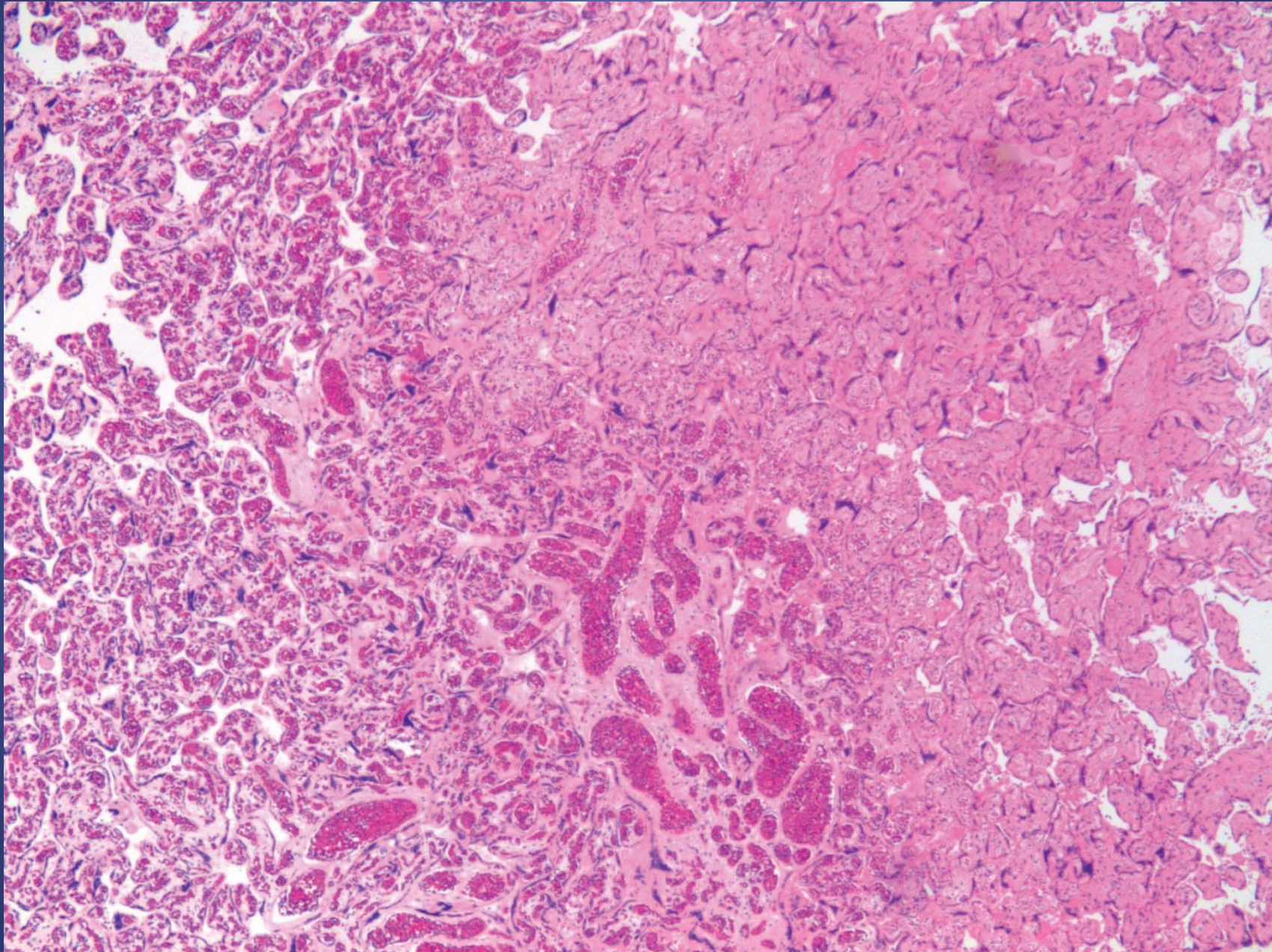
Blood beneath or within decidua

Villous compression with crowding and
congestion

Intravillous hemorrhage

Coagulative necrosis of syncytiotrophoblast

Infarction Above Retroplacental Hemorrhage



Amsterdam 2014 Consensus Terminology

- Fetal Vascular Malperfusion

Preferred over “Thrombotic Vasculopathy”

Umbilical cord lesions

Thrombophilia

Cardiac dysfunction

Chronic thrombo-occlusive lesions in fetal circulation of the placenta due to chronic or sudden cessation of blood flow to distal chorionic villi.

Obstruction to *venous* drainage due to intermittent or chronic mechanical cord obstruction
much more common

- Overlong and often hypercoiled cords
- Nuchal or complex cord loops
- Tight Cord knots
- Velamentous cords

Obstruction to *anterograde* arterial blood flow associated with:

- 2° fetal hypercoagulable state (hypovolemia, erythrocythemia)
- Fetal cardiac dysfunction (decreased perfusion pressure)
- 1° fetal thrombophilia

Fetal Vascular Malperfusion

Chorionic Surface (Large) Vessel

Thrombosis (arterial or venous)

Vascular intramural fibrin deposition

(preferred over “intimal fibrin cushion”)

Vascular (venous) ectasia (fourfold vs. artery)

Distal (Small) Vessel

Stem vessel fibromuscular sclerosis/obliteration

(preferred over “endovasculopathy”)

Segmental avascular villi

Villous stromal-vascular karyorrhexis

(preferred over “hemorrhagic endovasculitis”)

Fetal Vascular Malperfusion

Segmental/Global Patterns

Segmental – complete occlusion with downstream obstruction to umbilical blood flow

Global – partial/intermittent obstruction, but widespread

Numerous small (< 5 villi/focus) of avascular or karyorrhectic villi

Intramural fibrin deposition

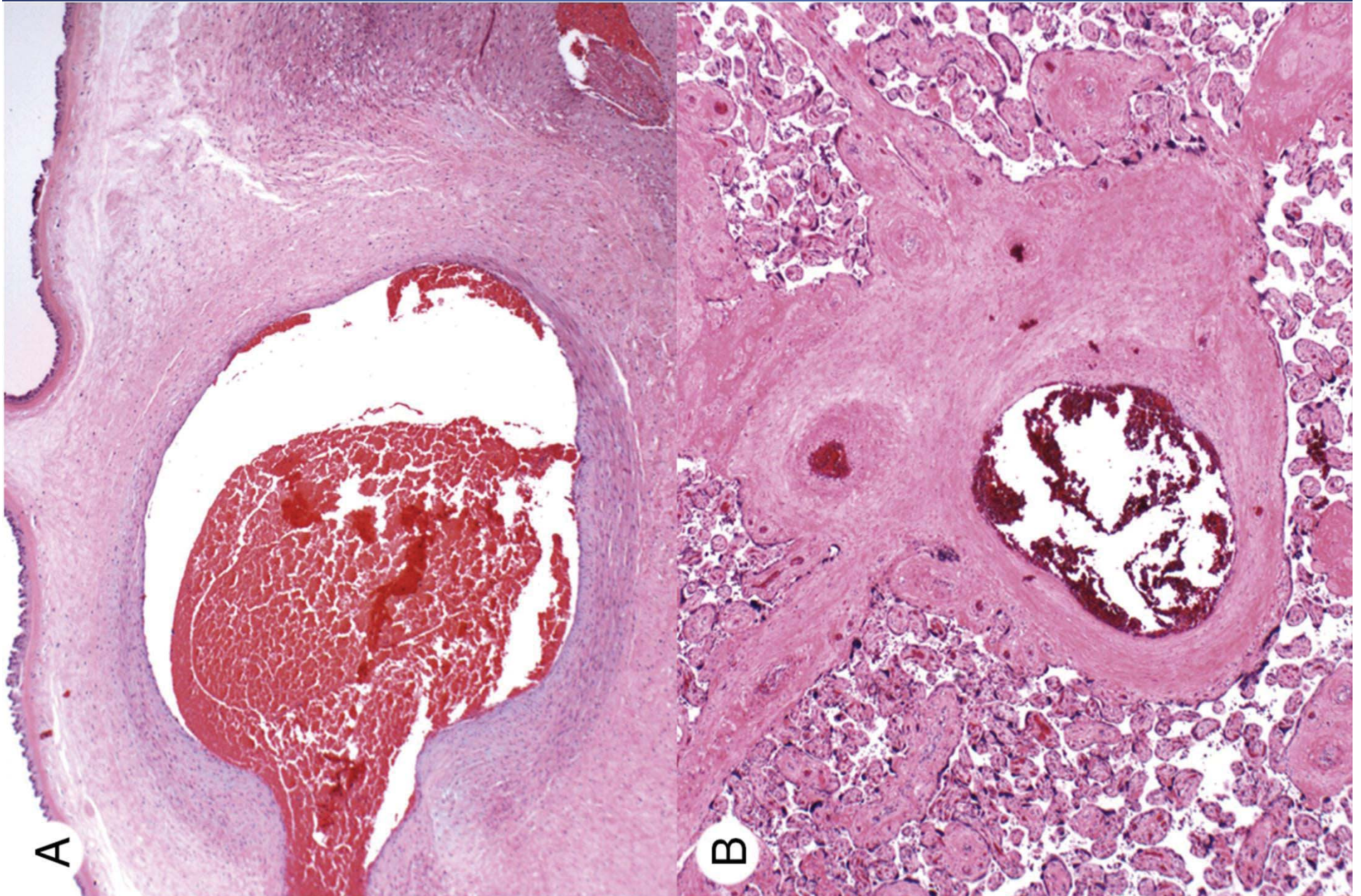
Venous ectasia

Umbilical Cord Thrombosis

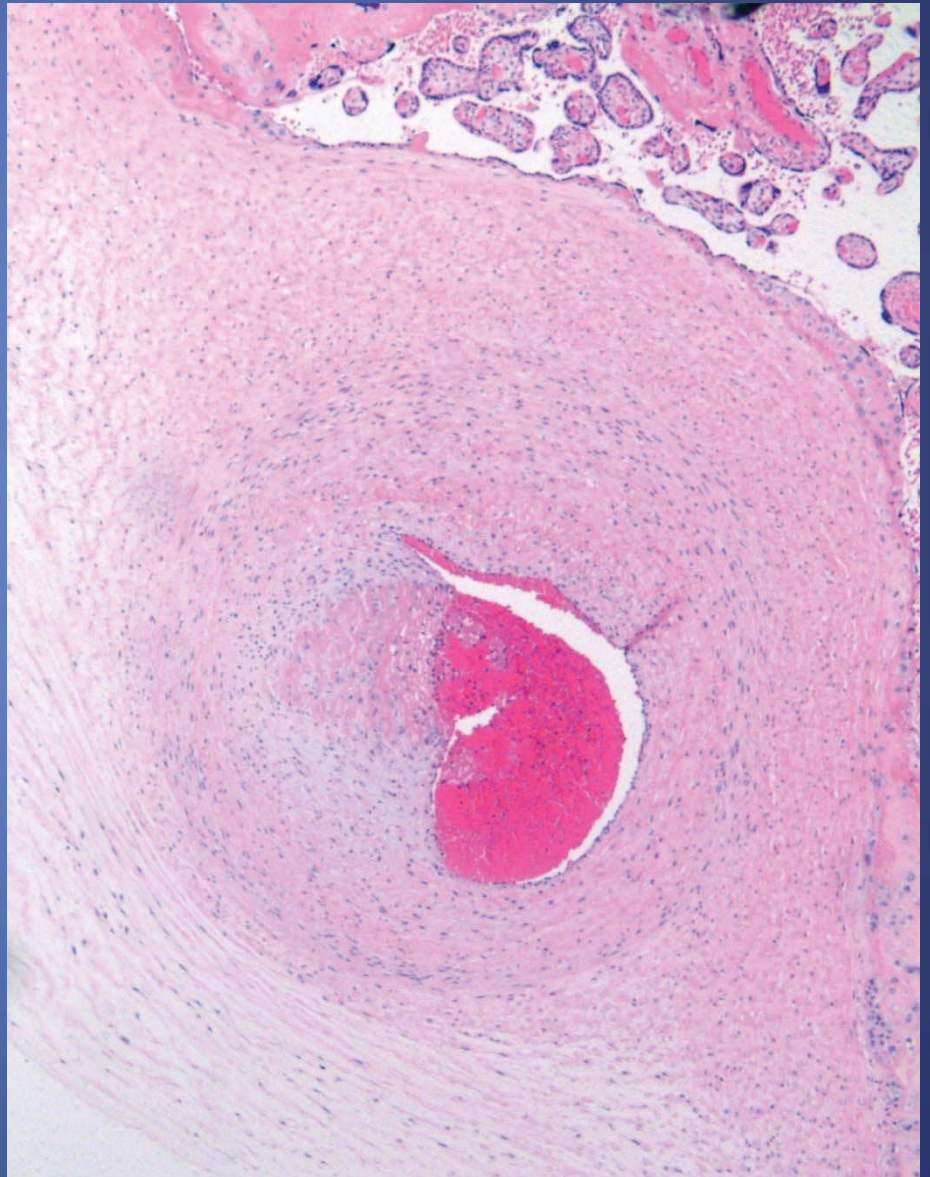
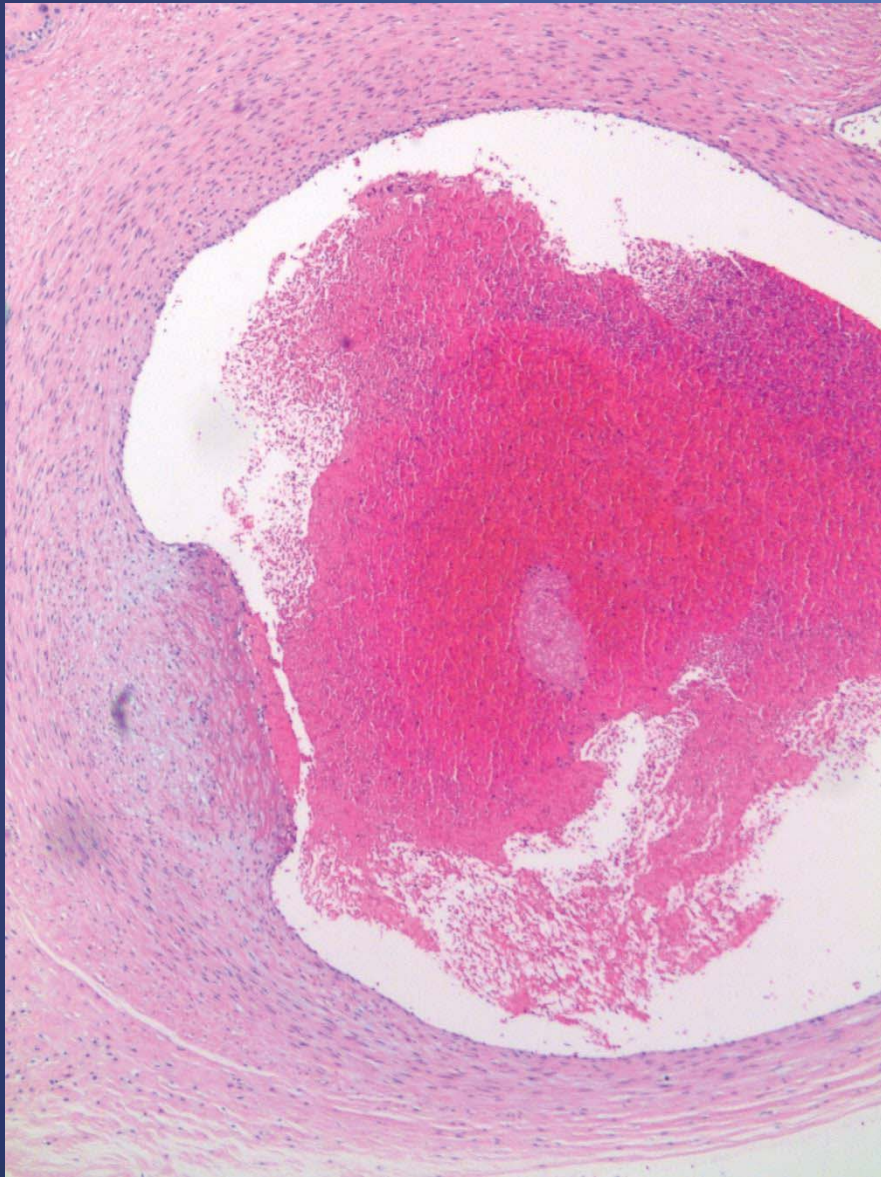


Chorionic and Stem Villous Venous Ectasia

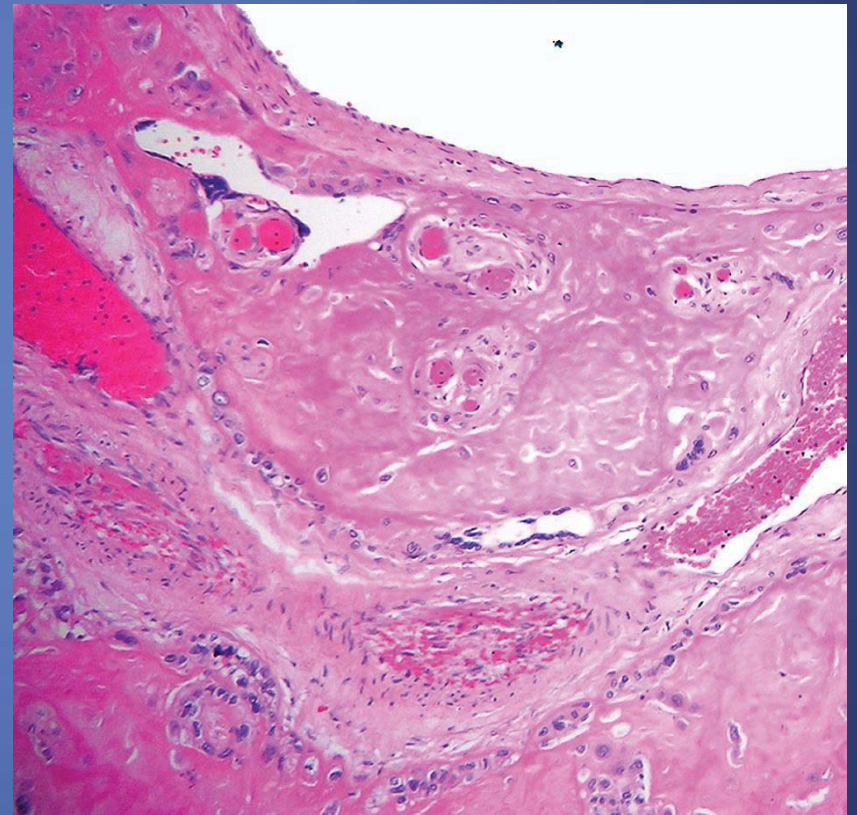
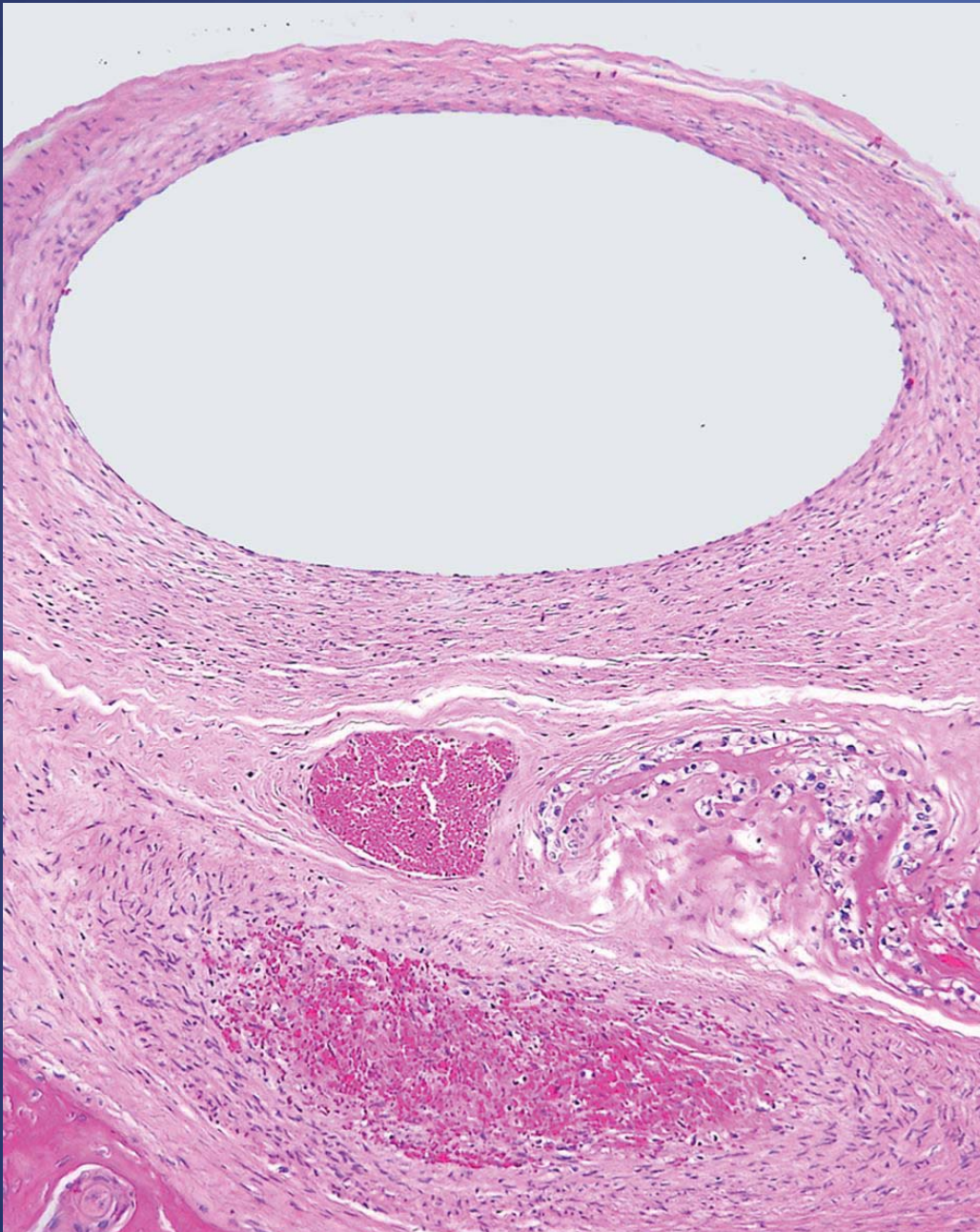
Parast, MM et al. Human Pathology, Volume 39, Issue 6, 2008, 948–953

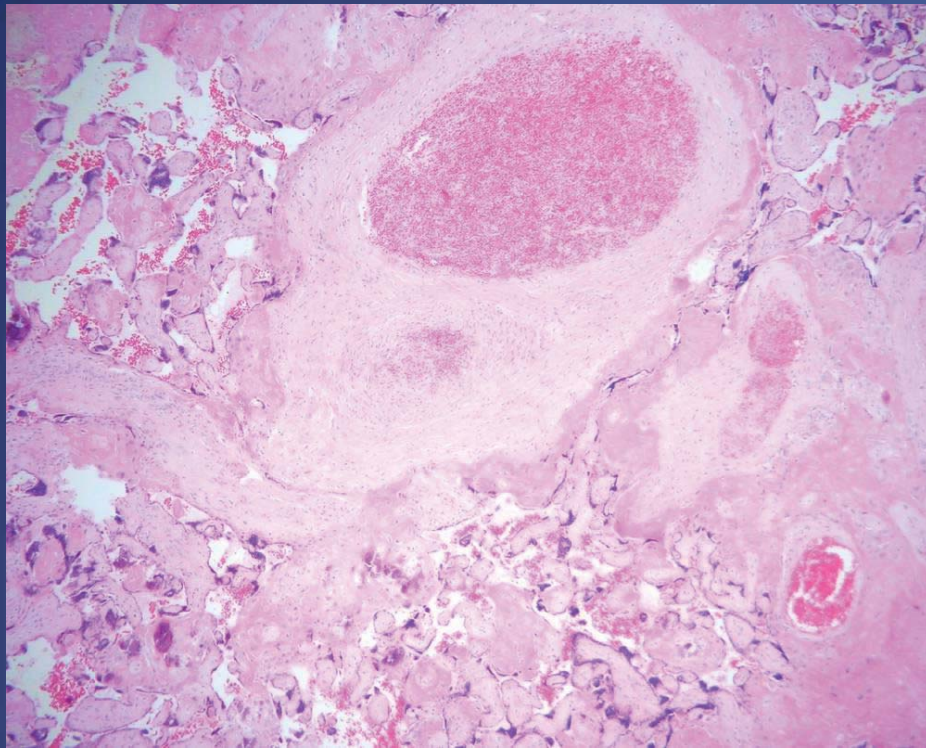


Chorionic Vascular Intramural Fibrin Deposition

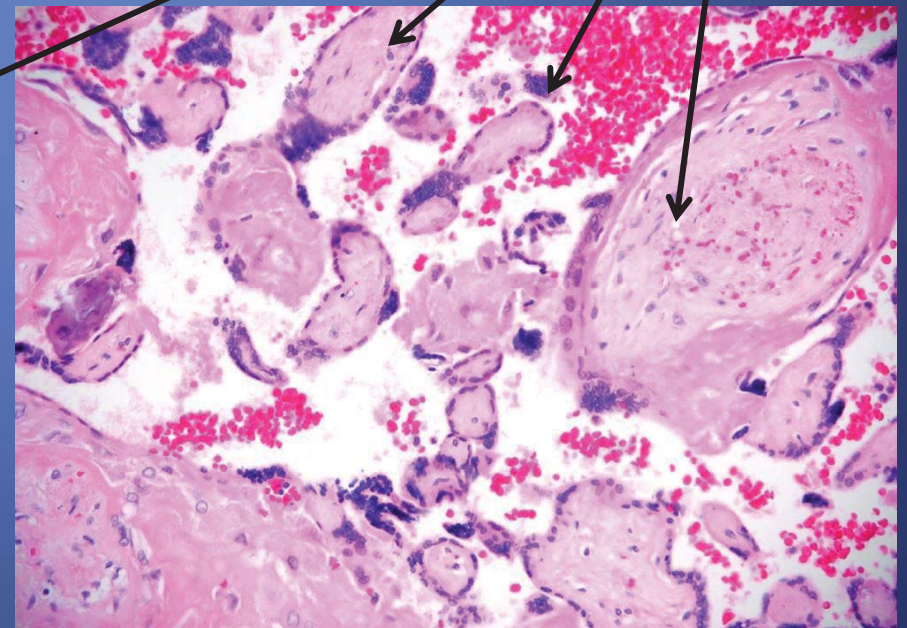
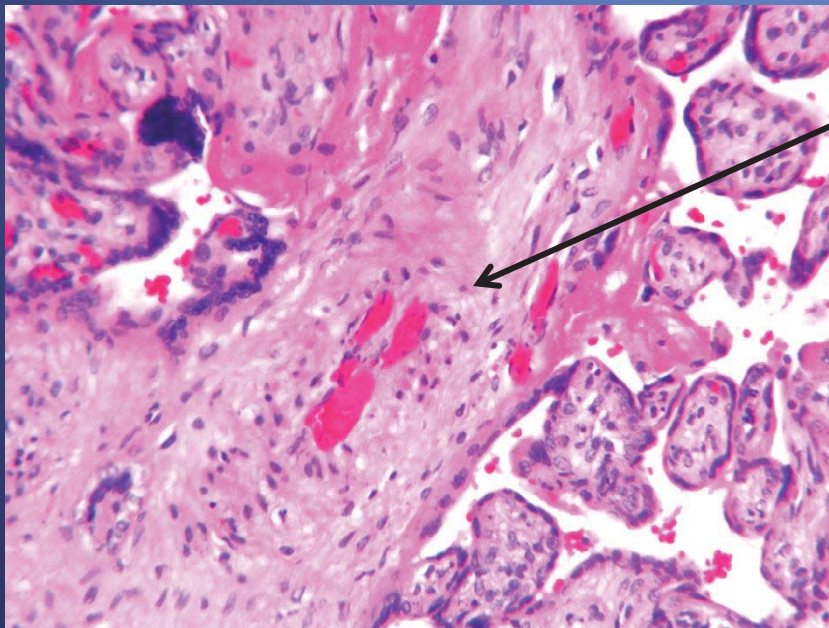


Chorionic and stem villous thrombi

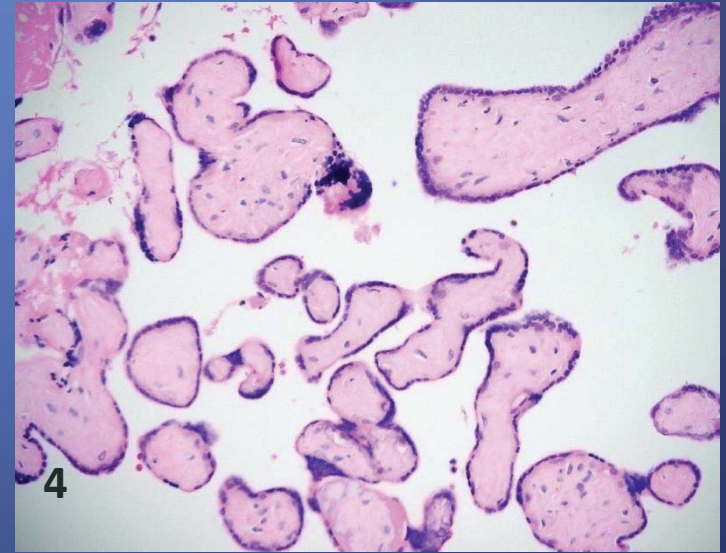
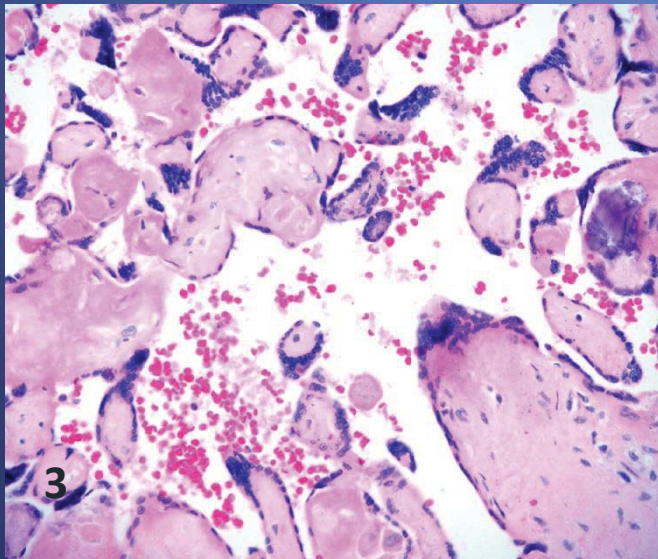
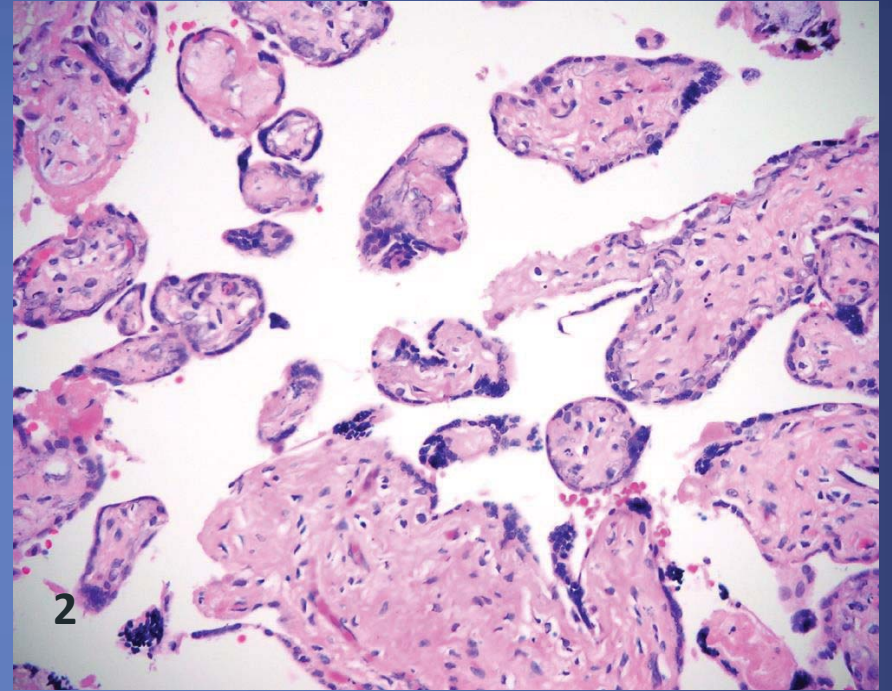
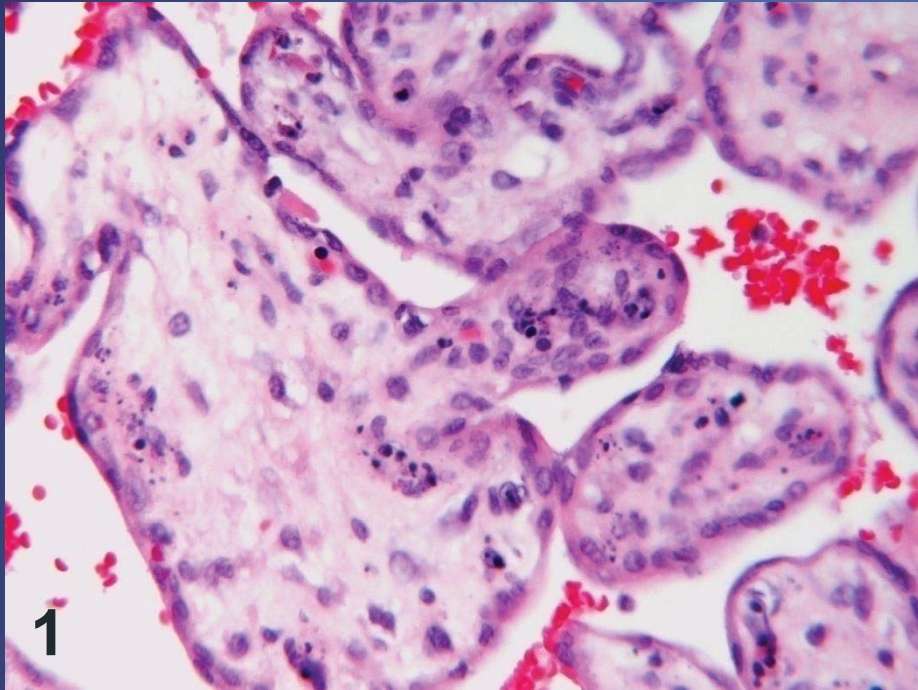




Thrombosis in chorionic villous tree → involutinal changes in dependent villi



Spectrum of Villous Changes with Fetal Vascular Malperfusion: Karyorrhexis to Diffuse Stromal Sclerosis



Fetal Vascular Malperfusion

Avascular/Karyorrhectic Villi Quantitation

Required for diagnosis: ≥ 3 foci of 2-4 affected villi

Intermediate foci: 5 -10 affected villi/focus

Large foci: > 10 affected villi/focus

Fetal Vascular Malperfusion

High Grade

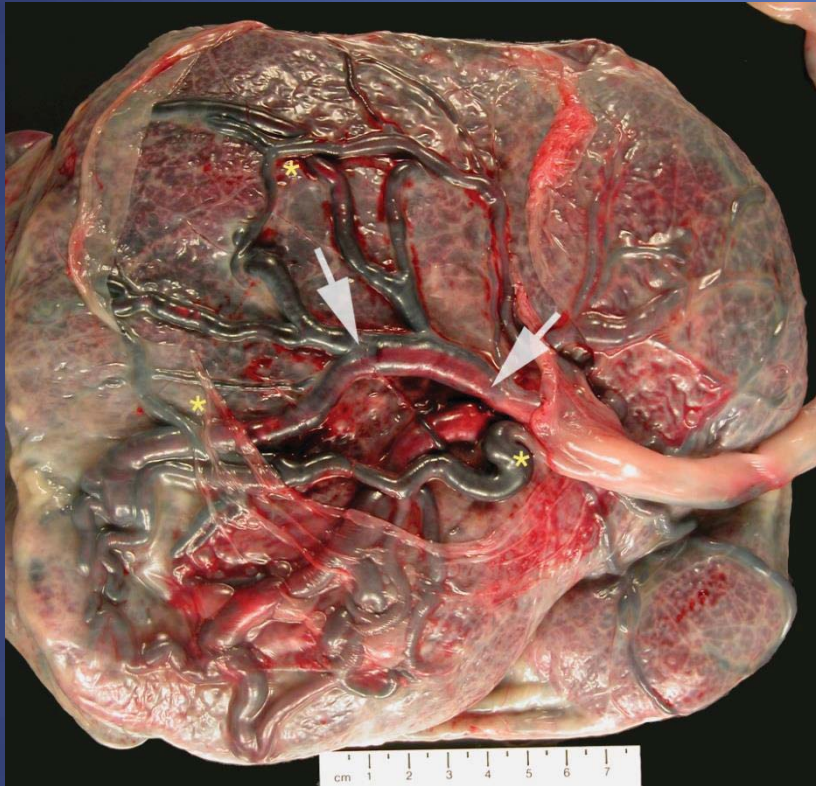
> 1 focus of avascular villi with ≥ 45 cumulative affected villi over 3 sections or averaging >15 affected villi; with or without thrombus

≥ 2 occlusive or non-occlusive thrombi in chorionic plate or major stem villi

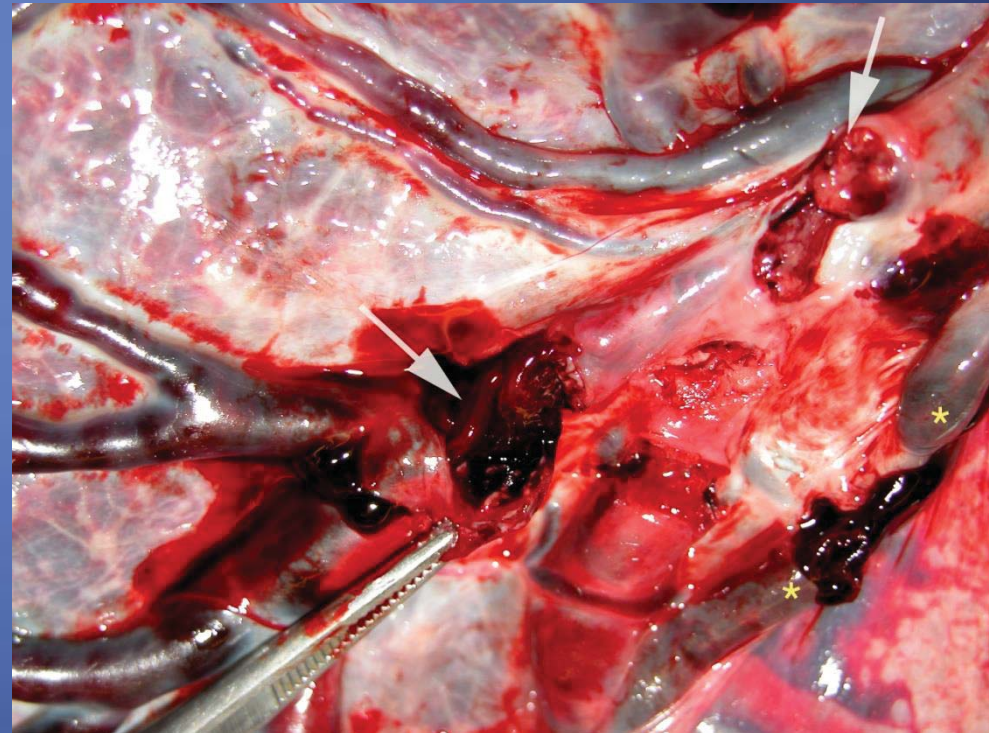
Umbilical cord thrombus

High Grade Fetal Vascular Malperfusion

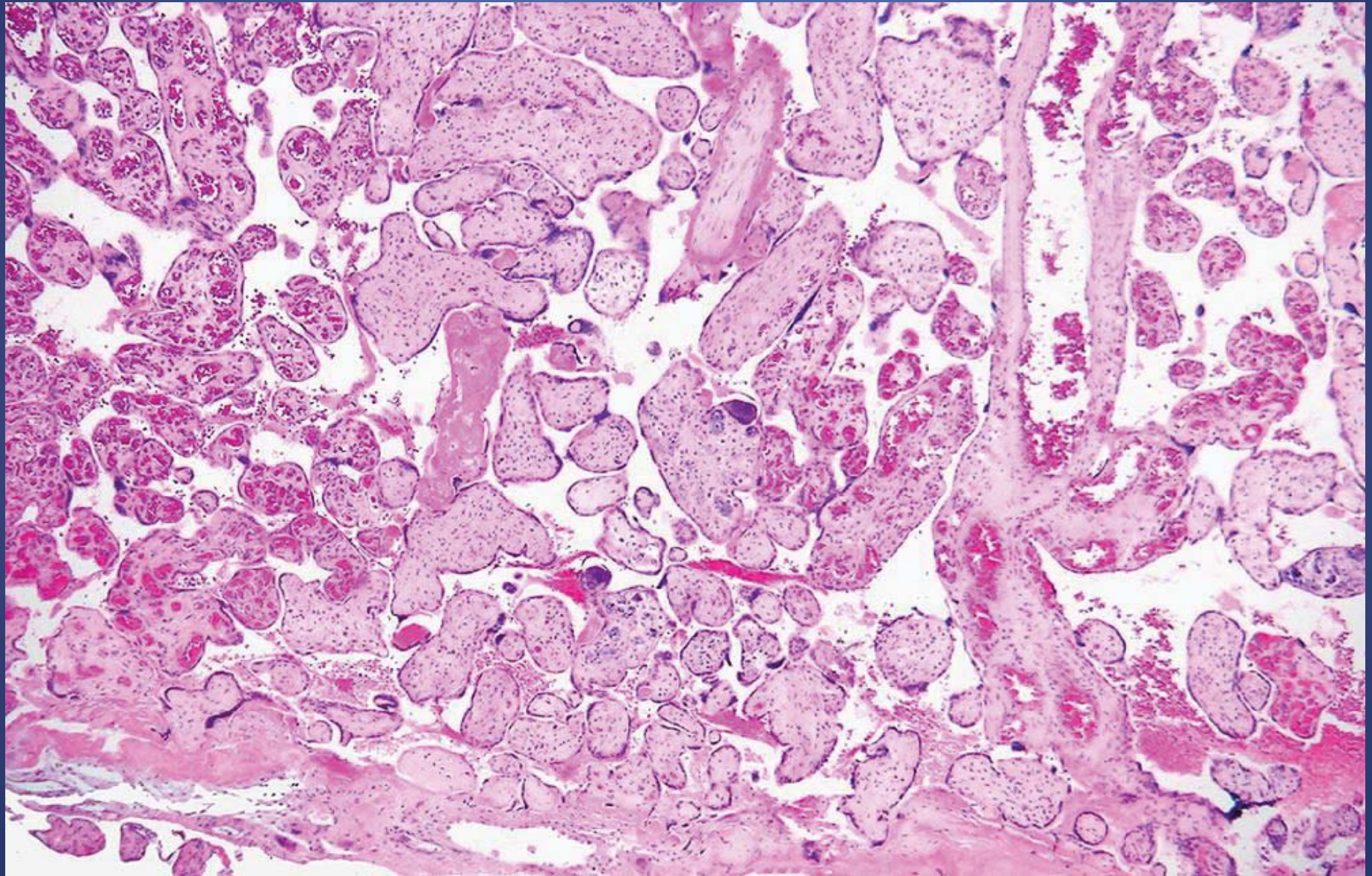
Chorionic Plate Thrombus



Chronic propagating
venous thrombi



High Grade Fetal Vascular Malperfusion
> 15 *Contiguous Avascular Fibrotic Villi*



Fetal Vascular Malperfusion

Associations:

- Impedance to blood flow in placenta (AEDBF)
- Fetal growth restriction (IUGR) related to loss of functional placental parenchyma
- Fetal demise, especially if extensive (30-50% of placental parenchyma)
- Thromboembolic phenomena in fetus
- Neurologic sequelae in liveborn infants

Postmortem placental involutinal changes of intrauterine retention can resemble *antemortem* pathology of Fetal Vascular Malperfusion

Multifocal stem villous vascular luminal abnormalities due to ingrowth of fibroblasts, resulting in “septation” and obliteration

Progressive terminal villous endothelial and stromal karyorrhexis, loss of capillaries, and sclerosis leading to a hyalinized appearance

Suggests premortem

Chorionic surface vessel thrombosis

Discreet population of avascular villi

Amsterdam 2014 Consensus Terminology

- Delayed Villous Maturation

Preferred over “dysmaturity or maturation defect”

Rare 34 weeks; usually after 36 weeks

Monotonous villous population (at least 10)

Centrally placed capillaries

Continuous cytotrophoblast layer

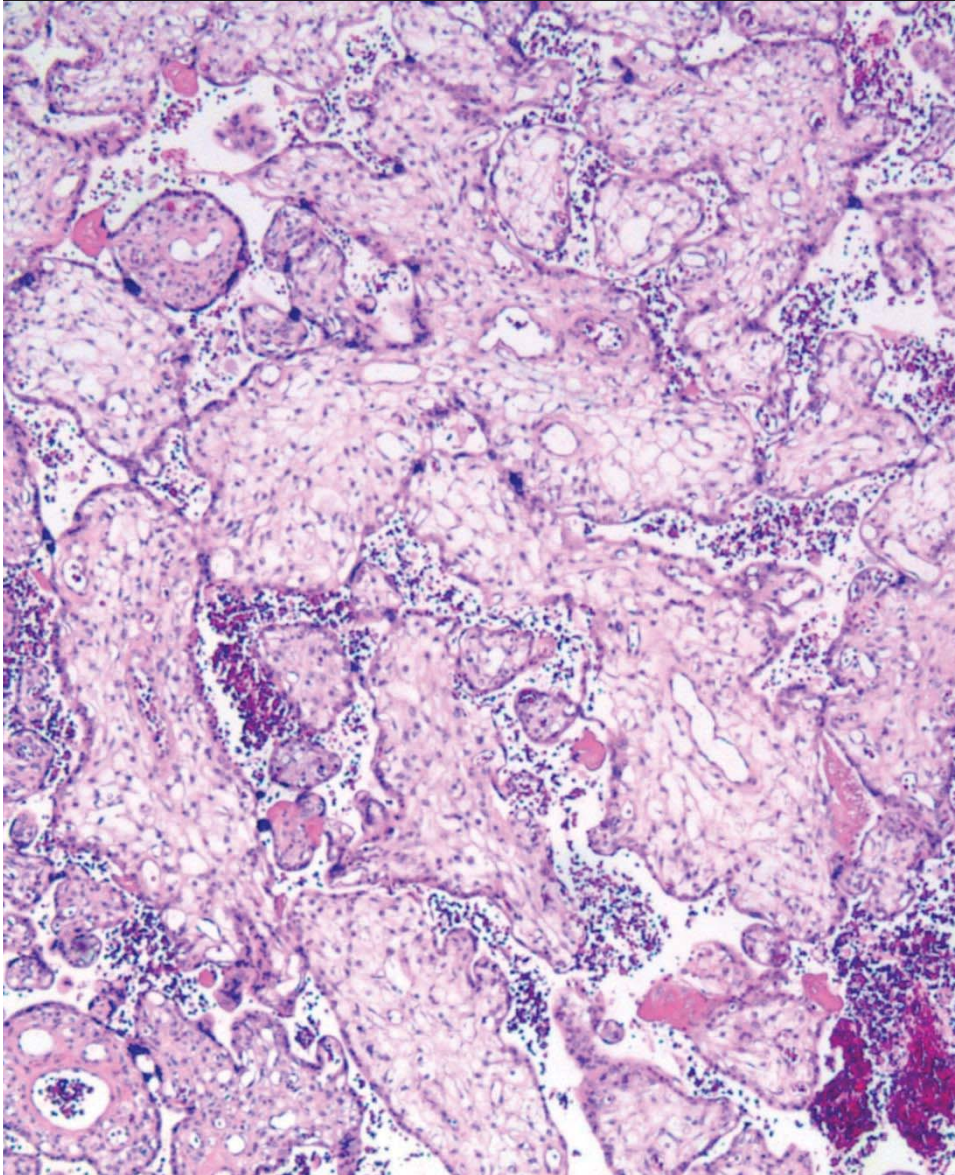
Decreased vasculosyncytial membranes

Focal: 30% of 1 full thickness section

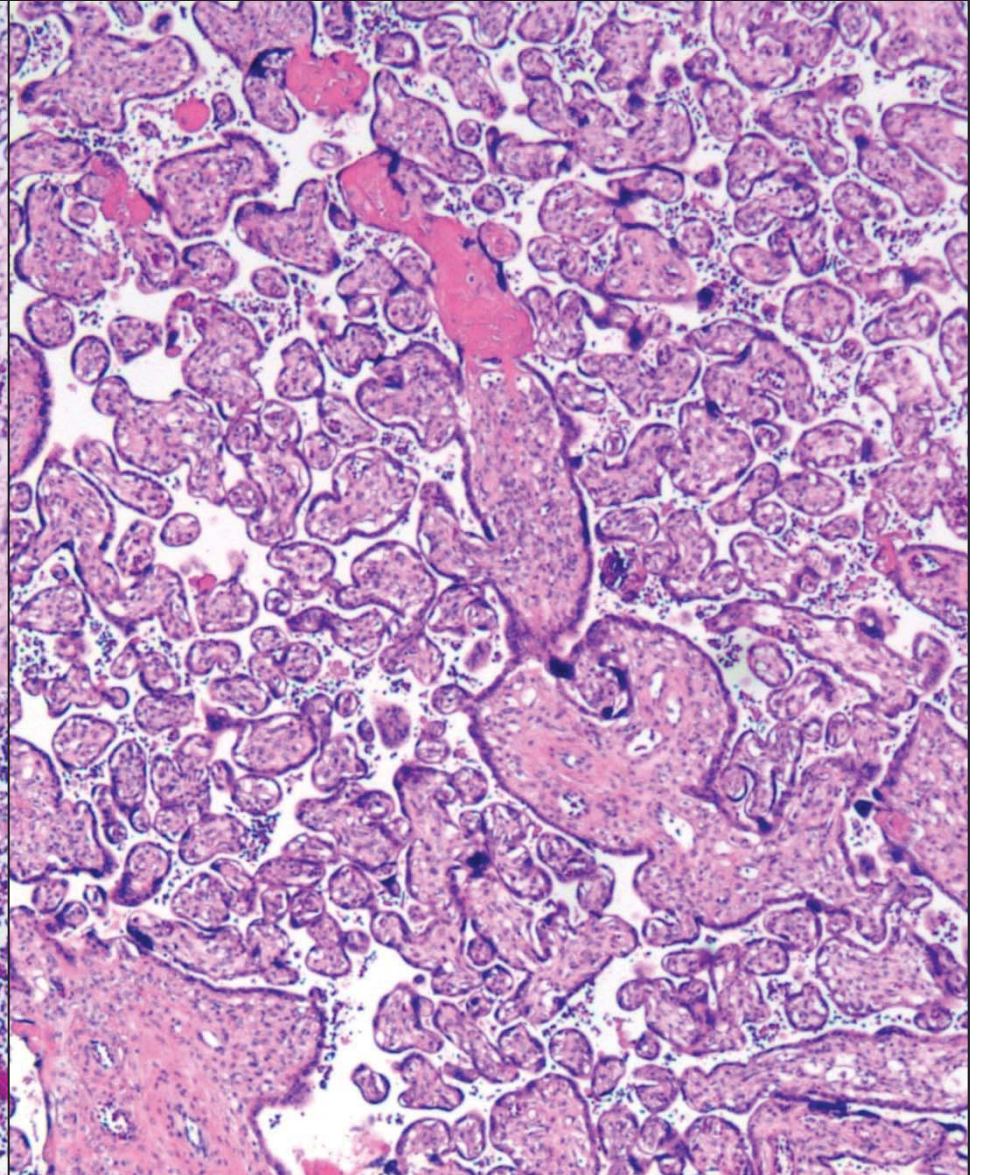
Diffuse: Present in more than one slide

Delayed Villous Maturation

Focal Delayed Villous Maturation



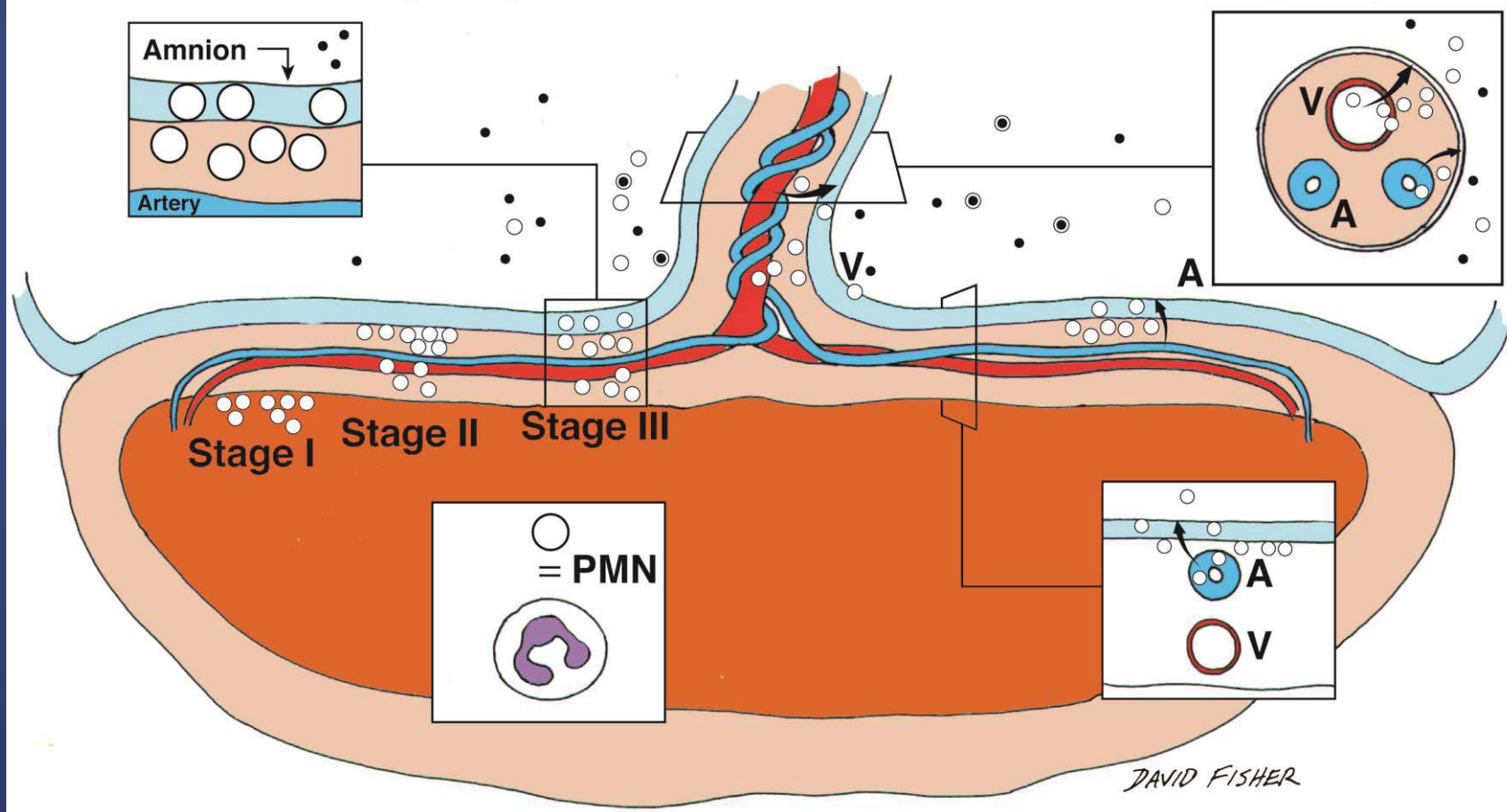
Adjacent Normal Villi 36 weeks



Ascending Intrauterine Infection

Maternal Inflammatory Response

Fetal Inflammatory Response



Chorioamnionitis/Funisitis

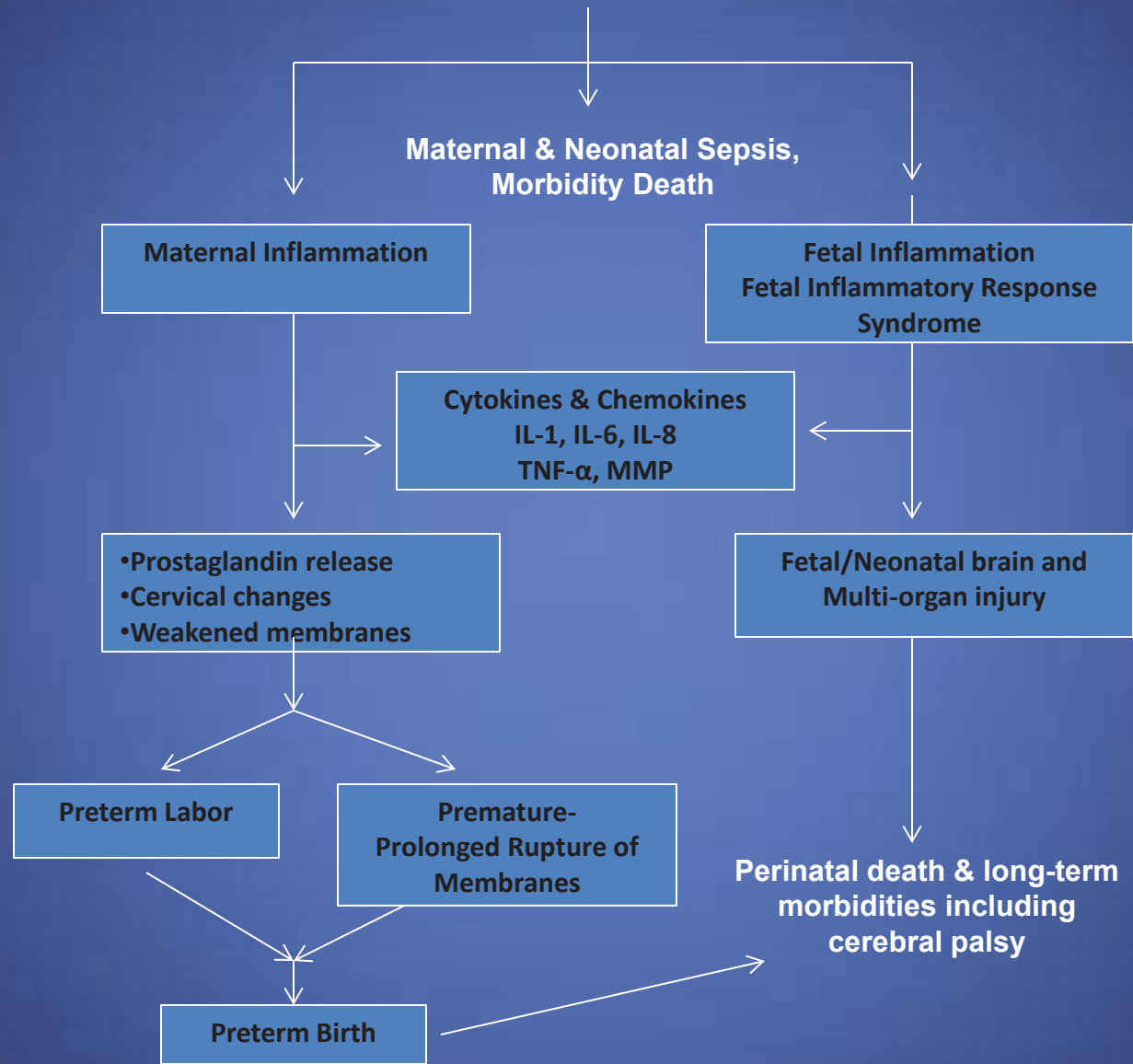


Fig 2, from: A. Tita, W. Andrews. Diagnosis and Management of Clinical Chorioamnionitis. Clin Perinatol. 2010; 37: 339-354

Ascending Intrauterine Infection

- Maternal Inflammatory Response

Stage 1 – acute subchorionitis or chorionitis

Stage 2 – acute chorioamnionitis: polymorphonuclear leukocytes extend into fibrous chorion and/or amnion

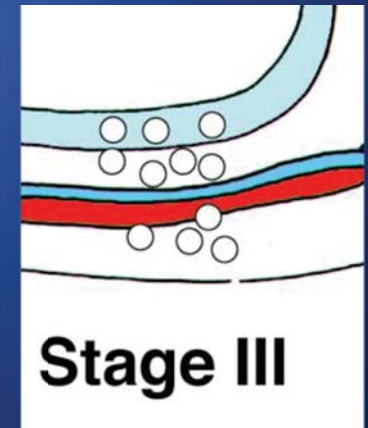
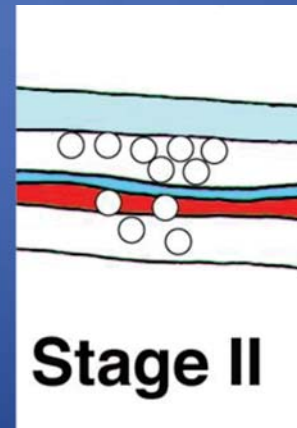
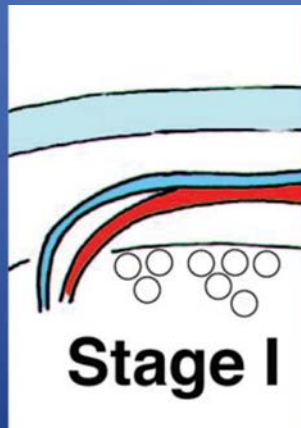
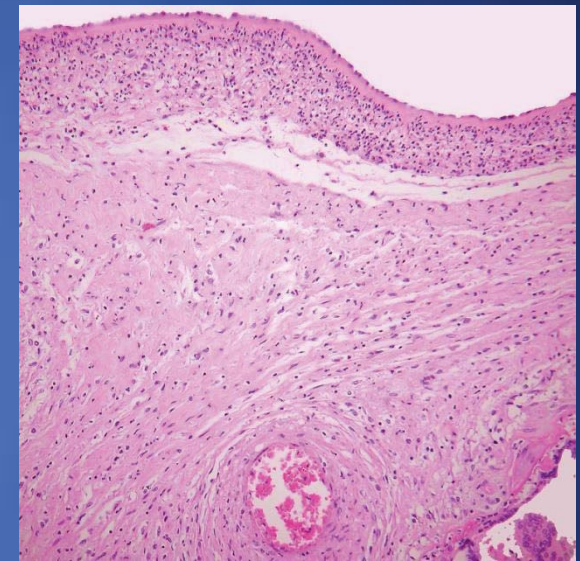
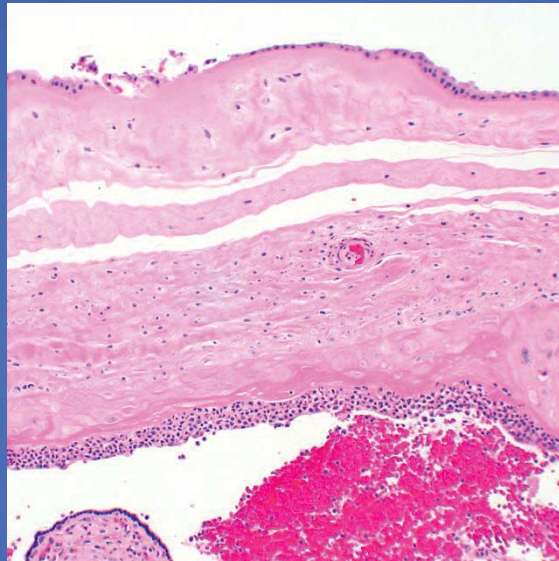
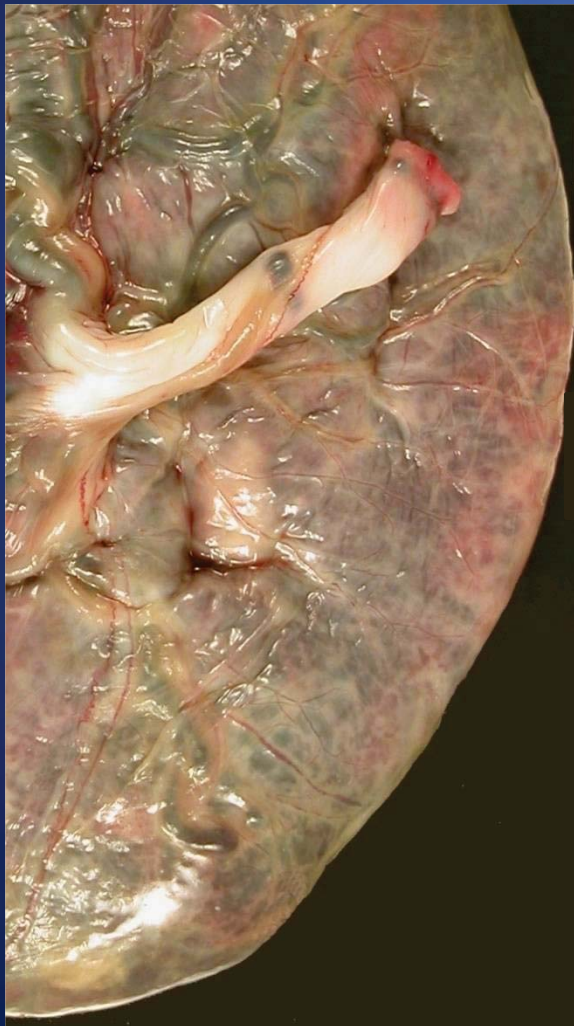
Stage 3 – necrotizing chorioamnionitis: karyorrhexis of polymorphonuclear leukocytes, amniocyte necrosis and or amnion basement membrane hypereosinophilia

Grade 1 – not severe as defined

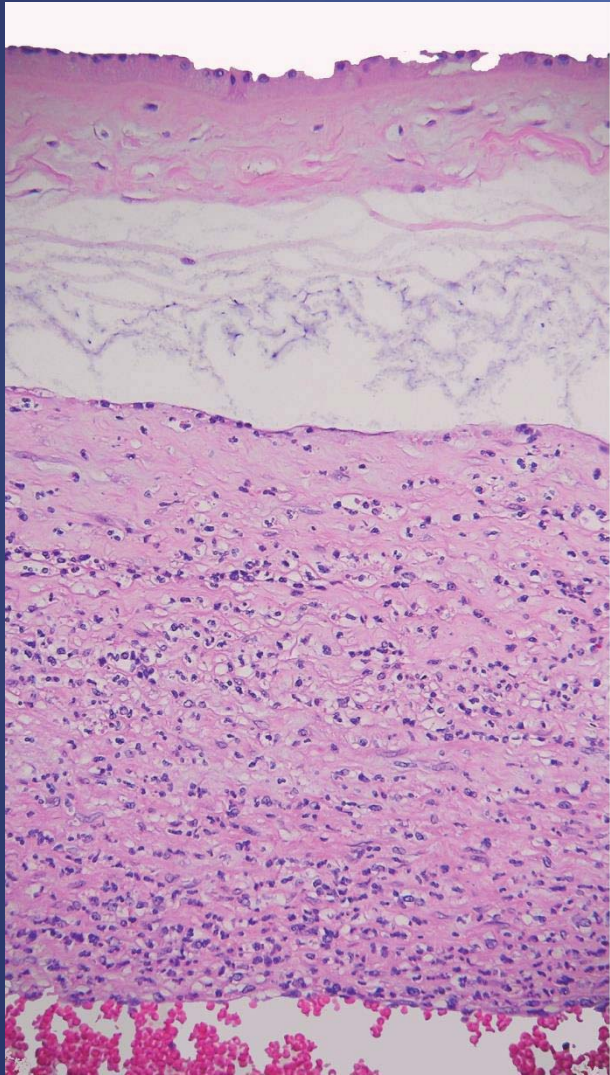
Grade 2 – severe: confluent polymorphonuclear leukocytes or with subchorionic microabscesses

Acute Chorioamnionitis

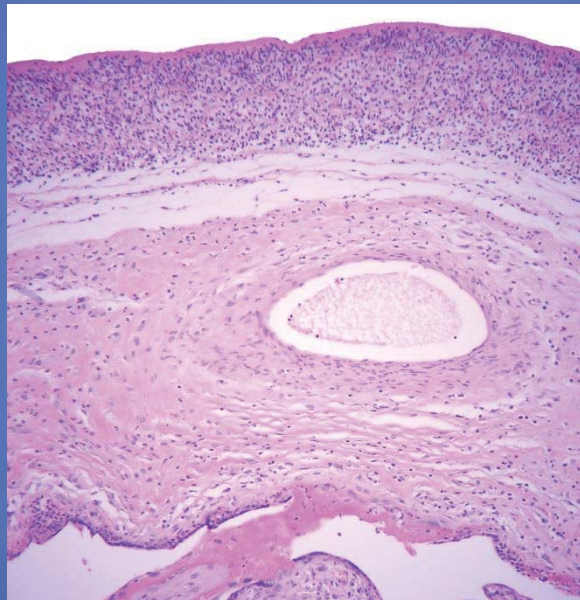
Maternal Inflammatory Response



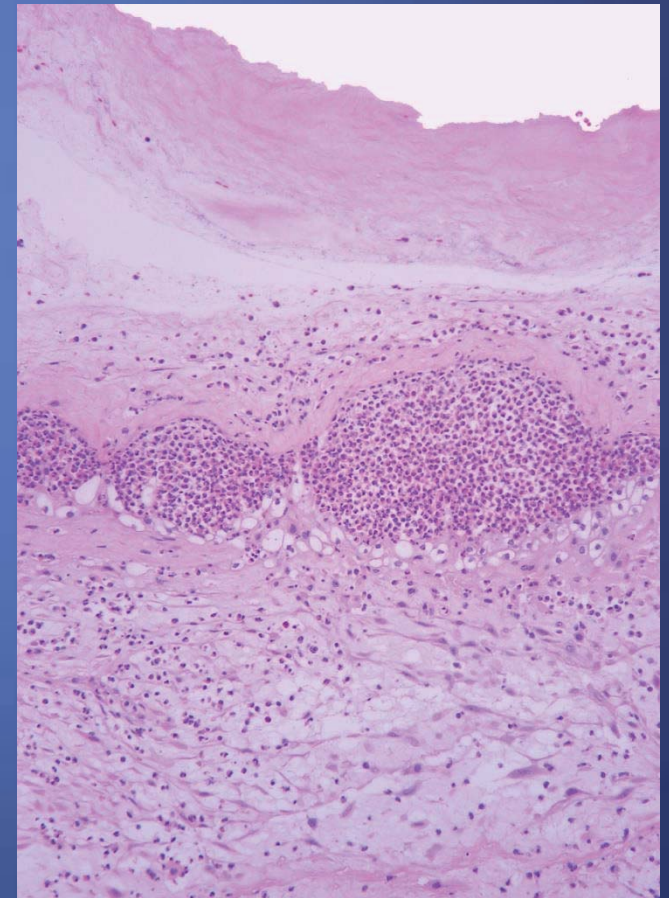
Maternal response
Stage 2



Maternal response
Stage 3 Grade 2
(severe)



Maternal response
Grade 2
(severe)



Ascending Intrauterine Infection

- Fetal Inflammatory Response

Stage 1 – chorionic vasculitis or umbilical phlebitis

Stage 2 – involvement of the umbilical vein and one or more umbilical arteries

Stage 3 – necrotizing funisitis

Grade 1 – not severe as defined

Grade 2 – severe: near-confluent intramural polymorphonuclear leukocytes with attenuation of vascular smooth muscle

Fetal Inflammatory Response

Chorionic vasculitis

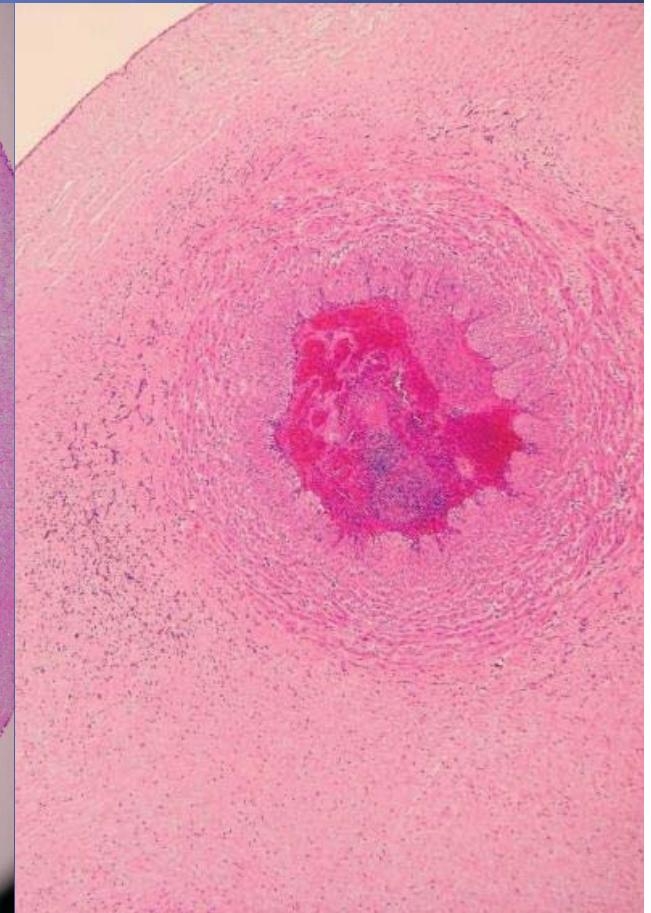
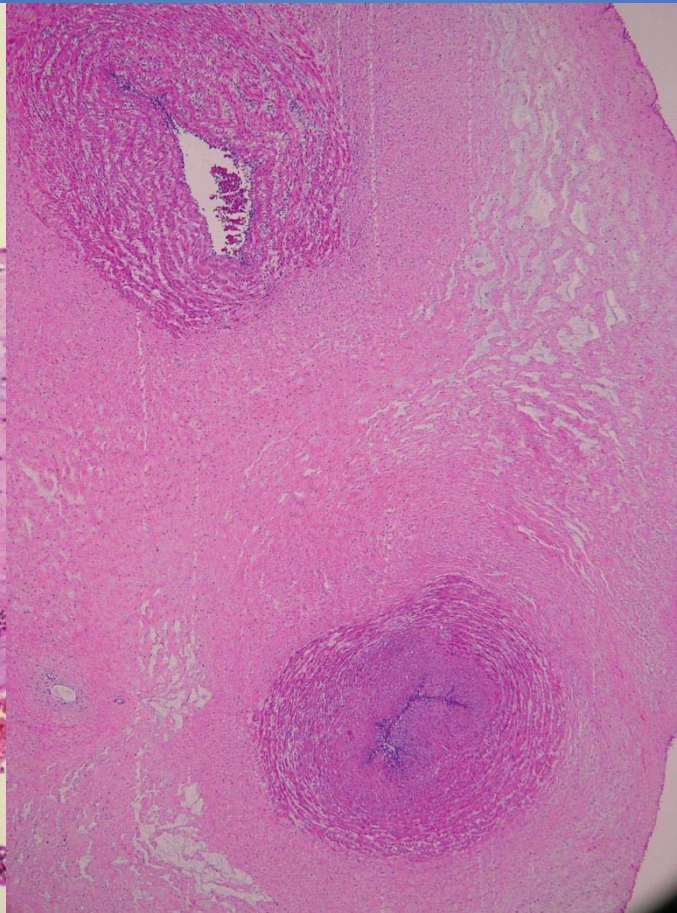
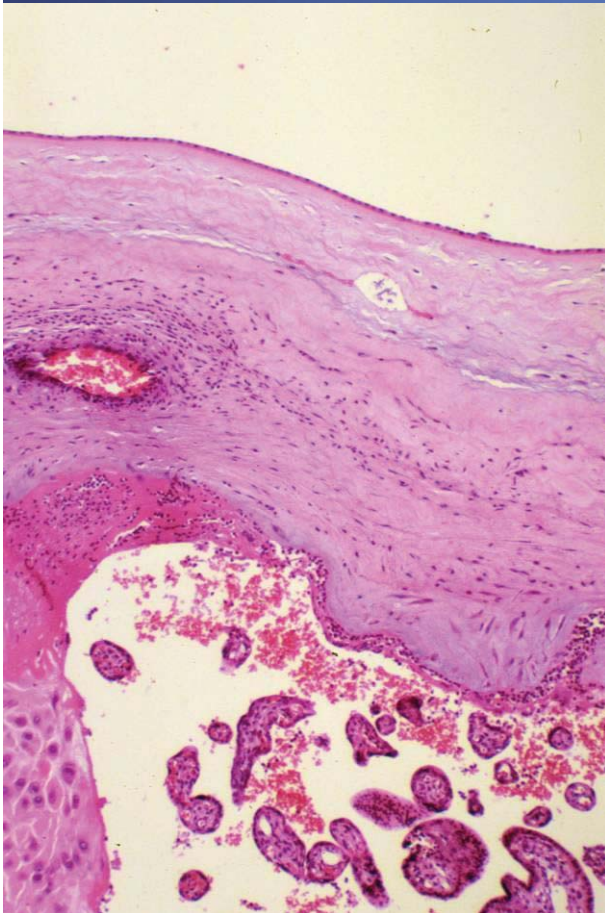
Stage 1= intramural PMNs

Funisitis = PMNs in cord

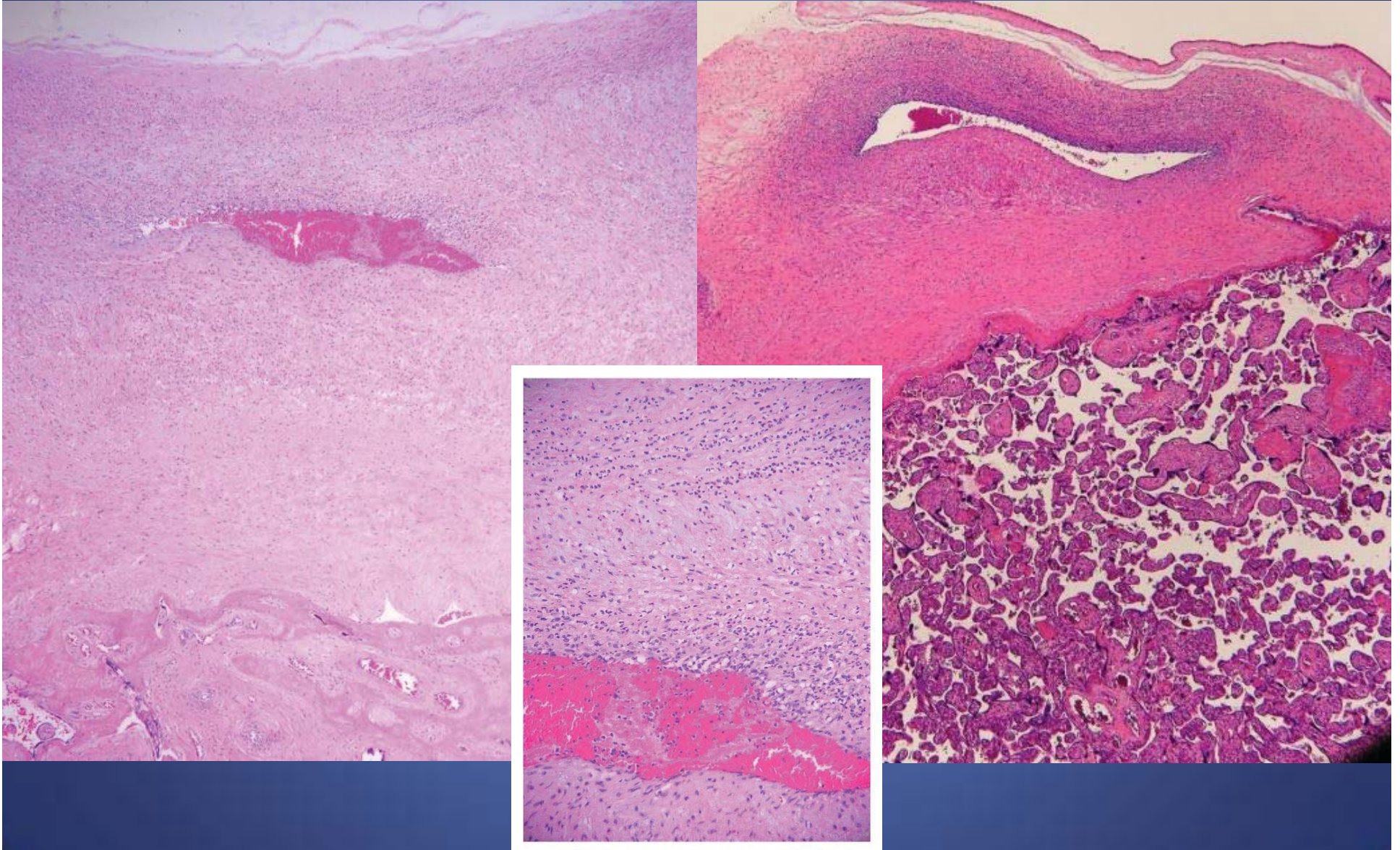
Stage 1= phlebitis intramural

Stage 2 = Vein + Art

Stage 3 = Necrotizing funisitis



Severe Fetal Inflammatory Response Grade 2

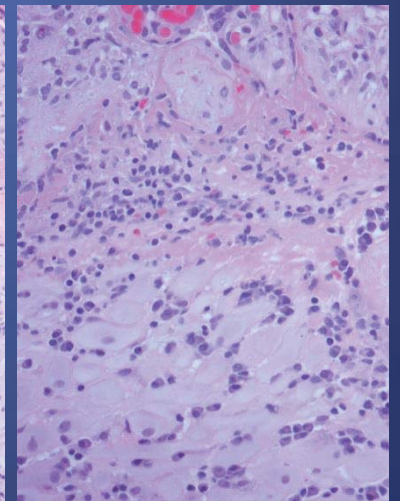
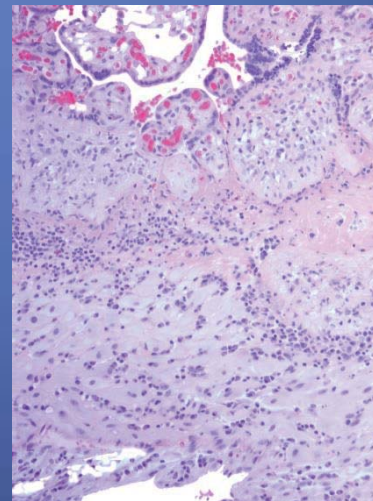
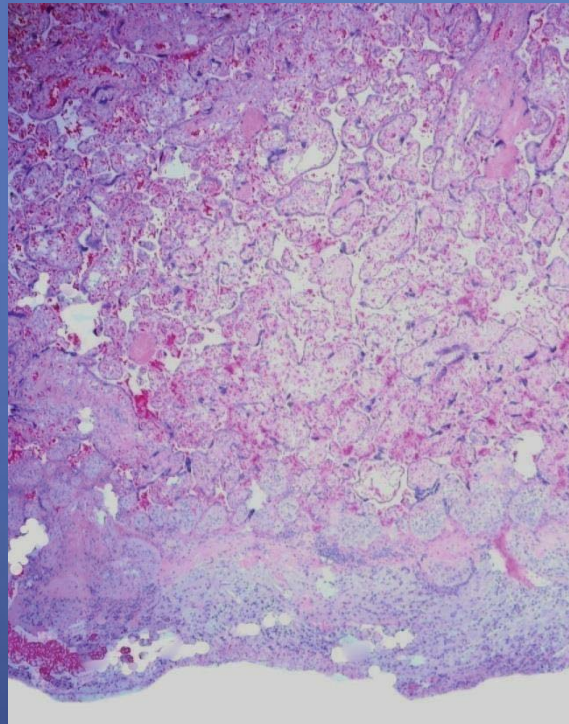
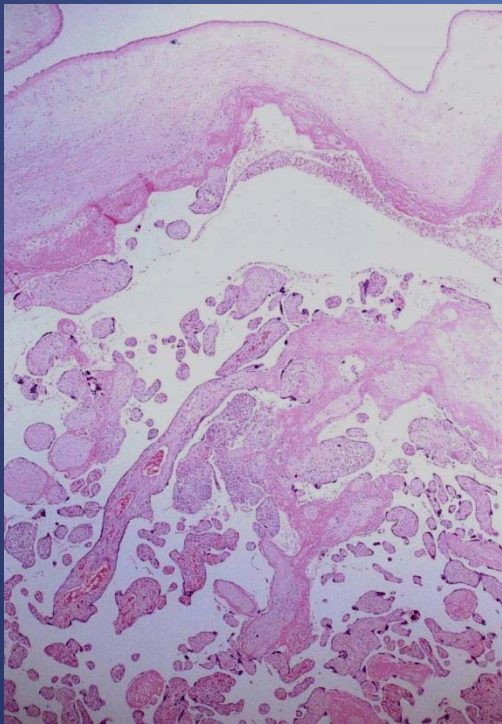


Villitis of Unknown Etiology

Subchorial and basal distributions typical

Often has maternal chronic lymphohistiocytic deciduitis

Spares stem villi and mid-parenchymal zone



Villitis of Unknown Etiology

- Low Grade

At least 2 foci; all with < 10 contiguous affected villi

Focal: Confined to one slide

Multifocal: More than one slide

Ungradable – possible low grade: Solitary focus < 10 contiguous villi

- High Grade

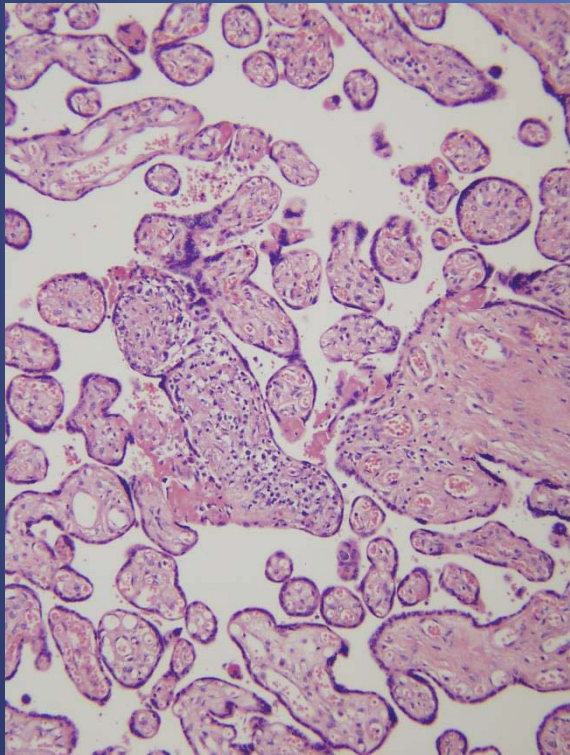
Multiple foci, >1 sections; at least one with > 10 contiguous affected villi

Diffuse: >30% of villi affected

Patchy: Not diffuse

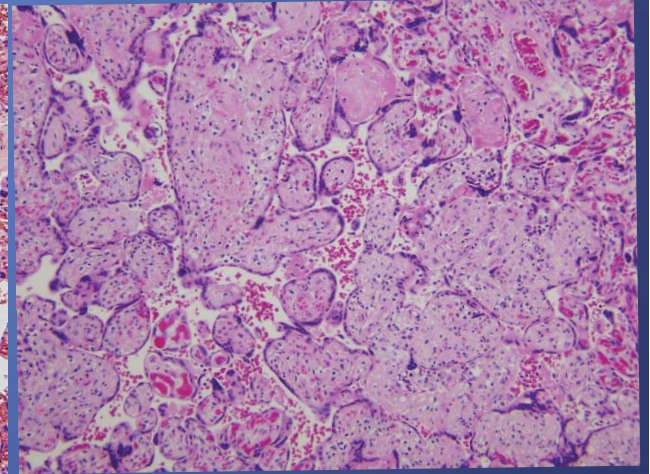
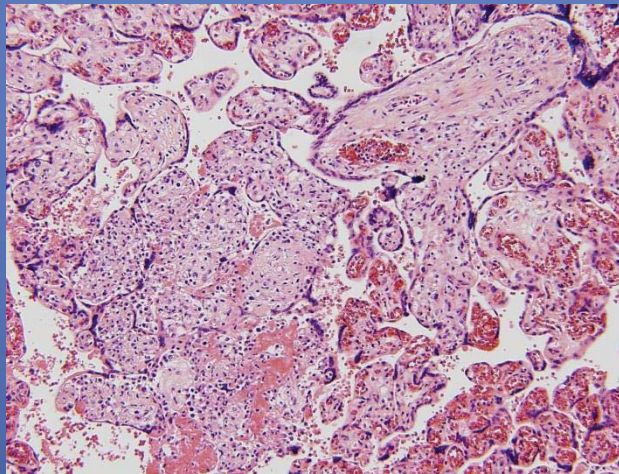
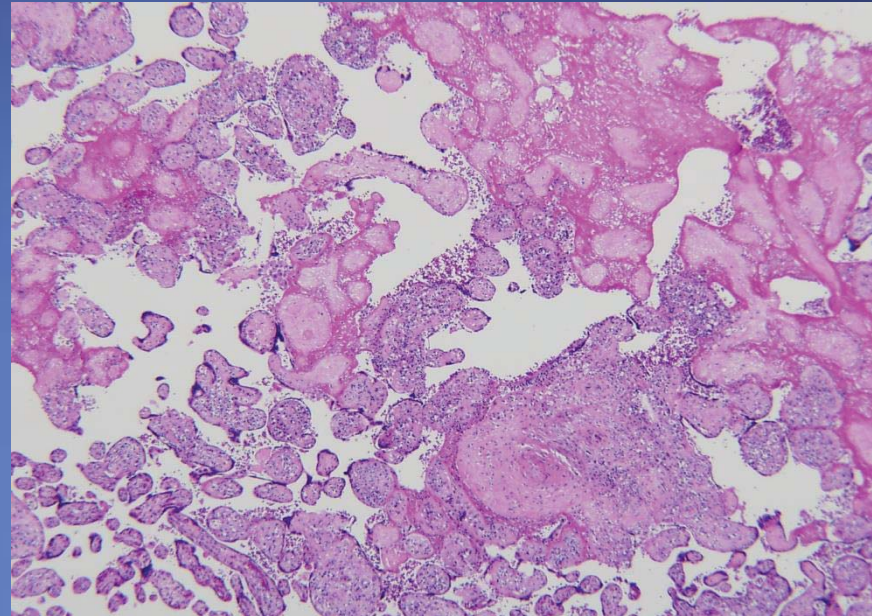
Ungradable – possible high grade: Solitary focus > 10 contiguous villi

Grading of Villitis of Unknown Etiology



Low grade VUE

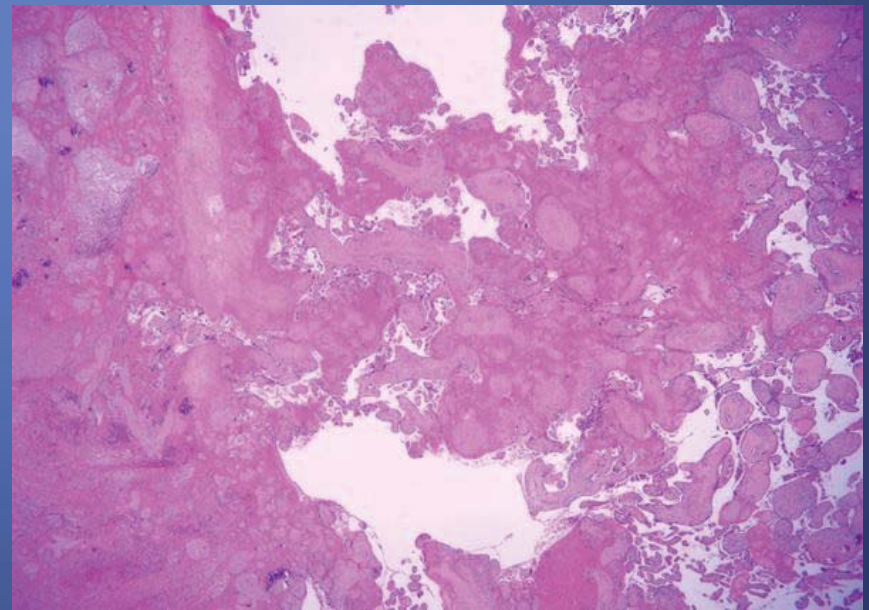
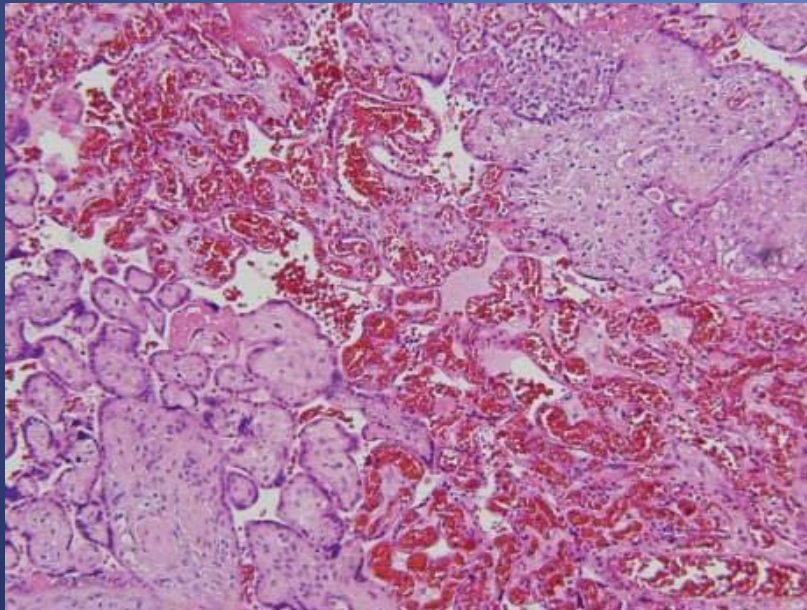
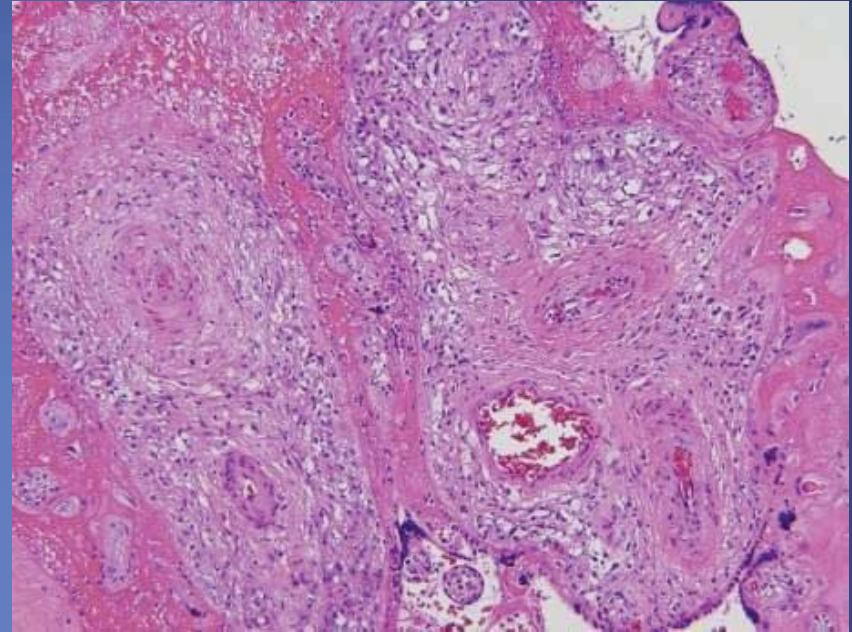
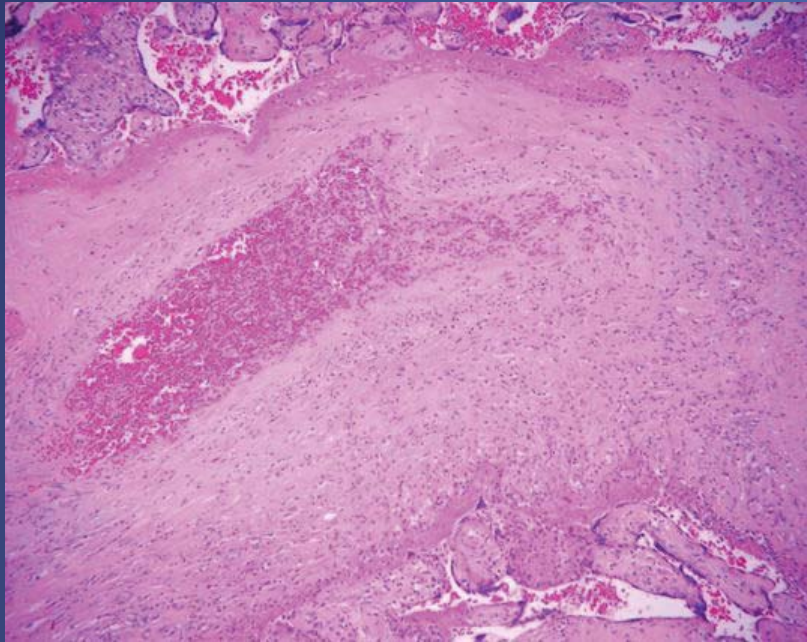
≤ 10 villi/ focus



High grade VUE

> 10 villi/ focus

Chronic Villitis with Stem Vessel Obliteration

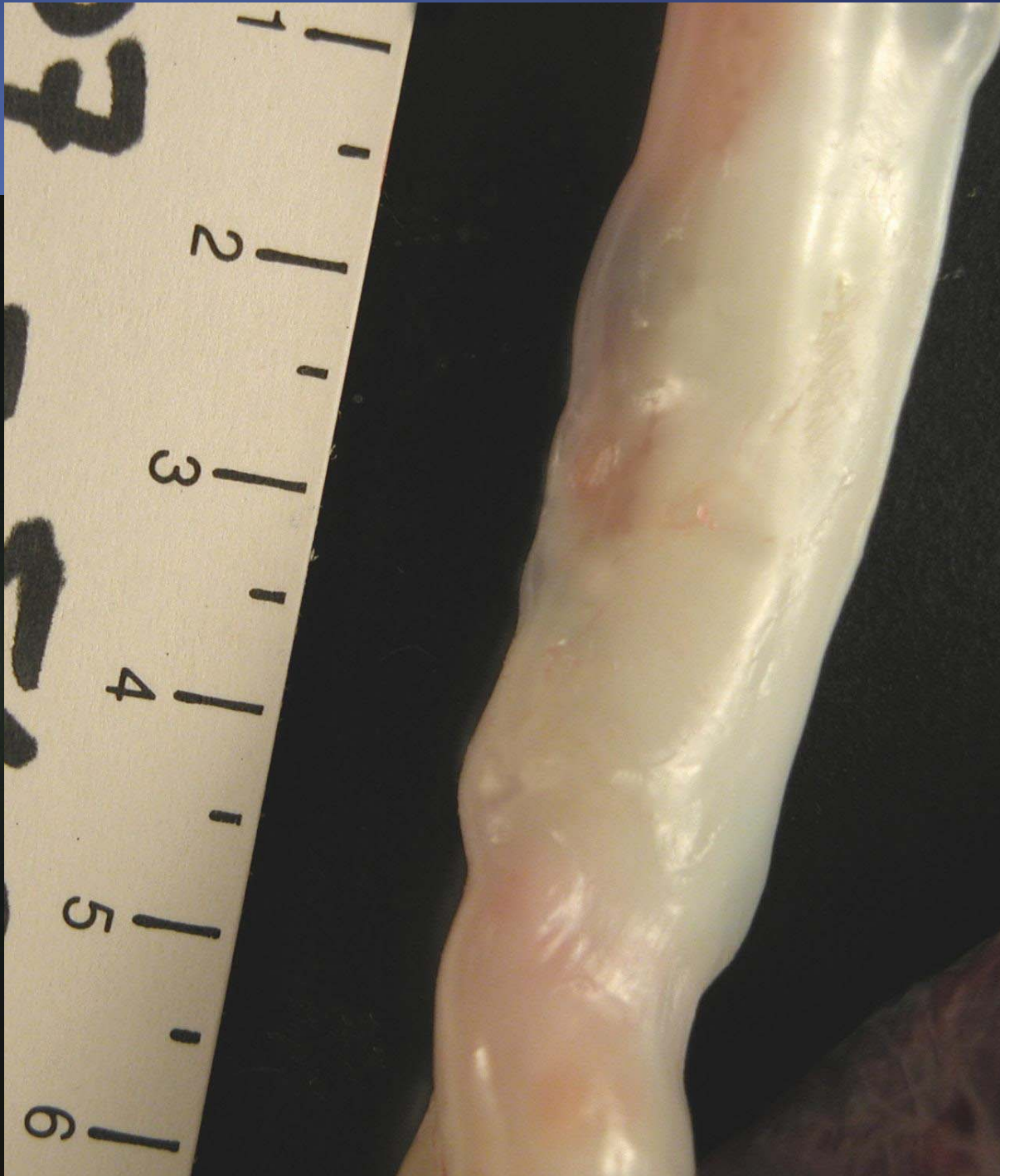
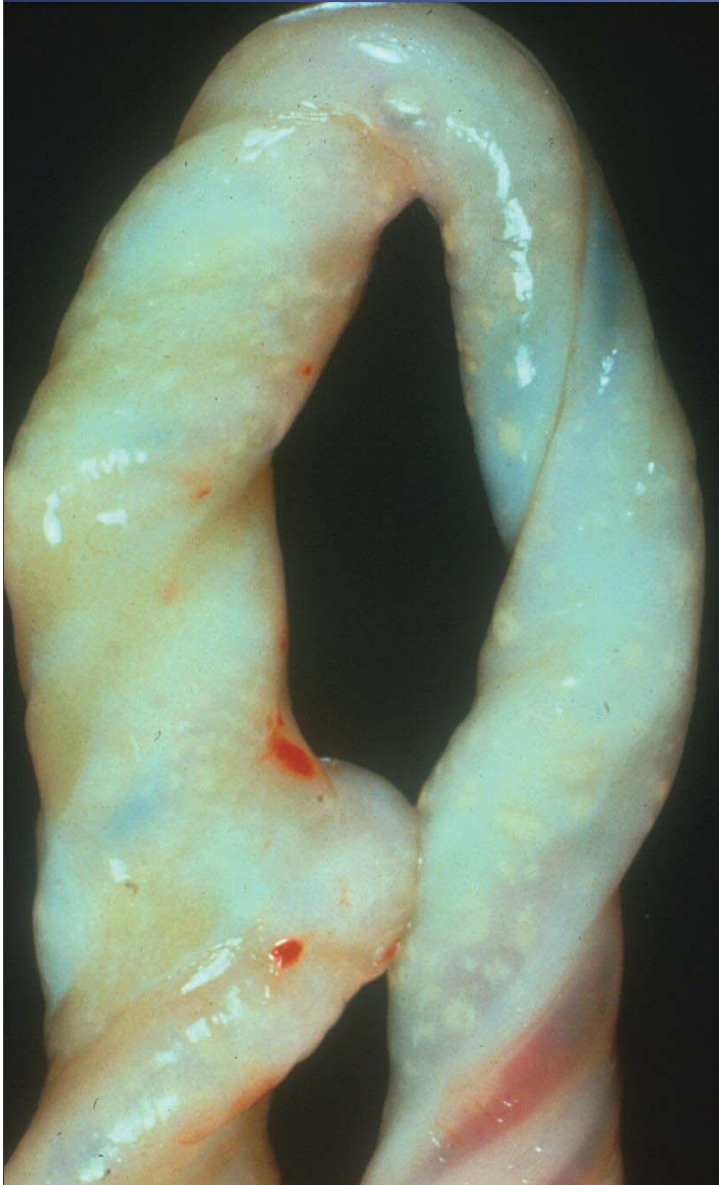


Placental “Critical Values”

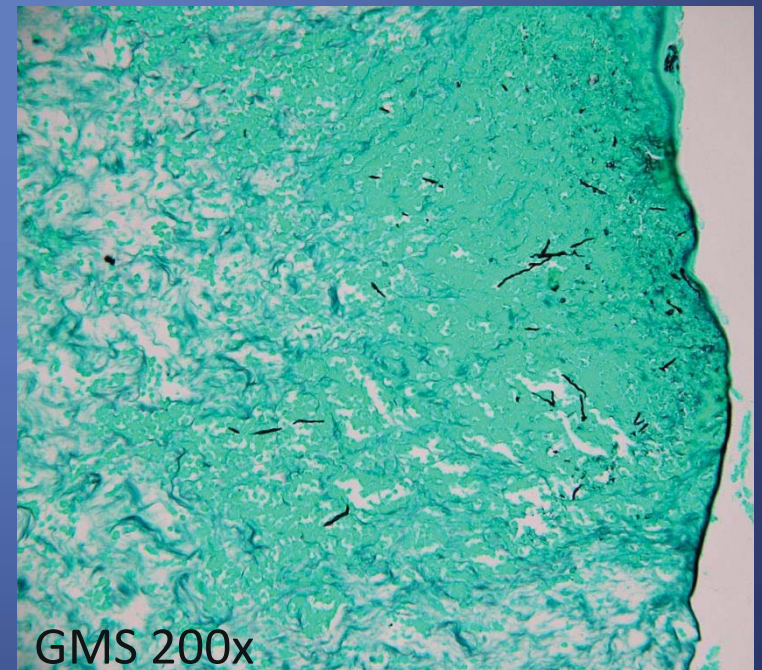
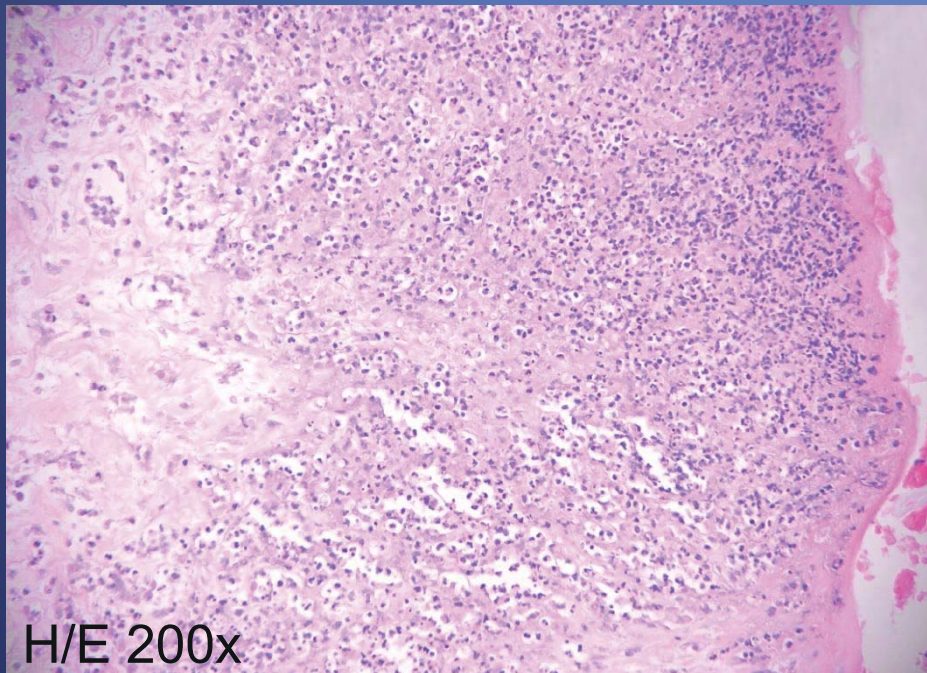
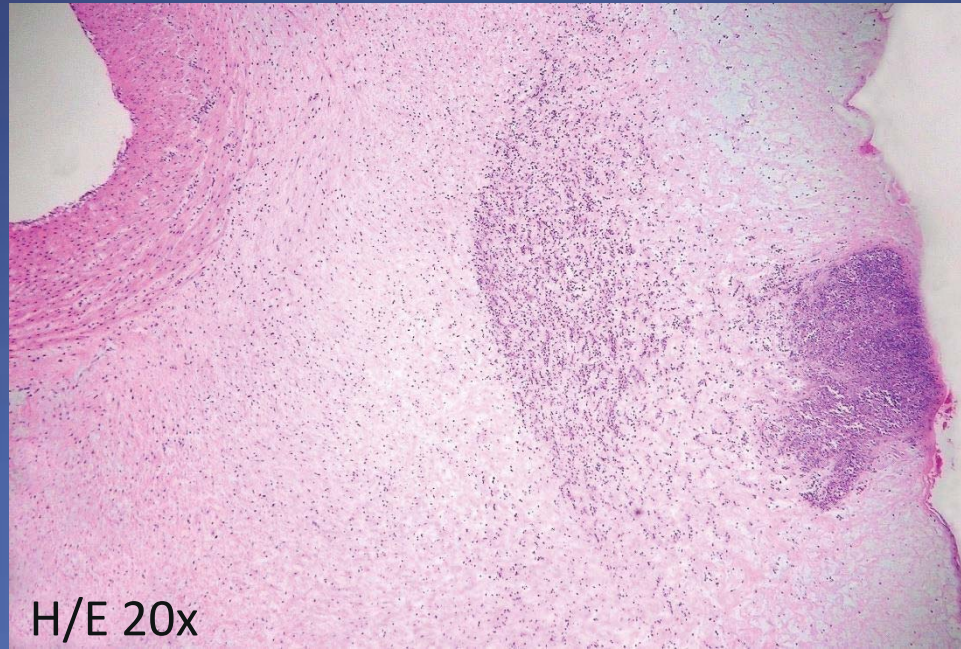
Gross Diagnoses:

Candida Funisitis

Candida Funisitis



Candida Funisitis

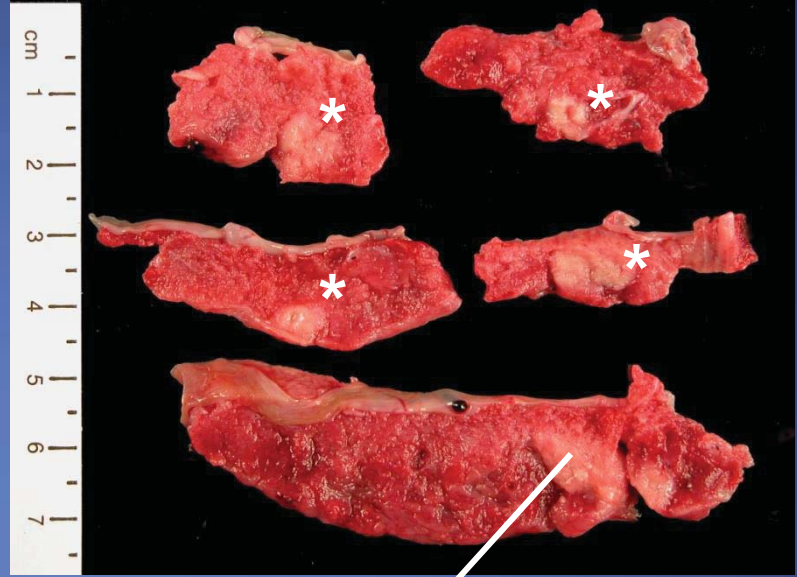
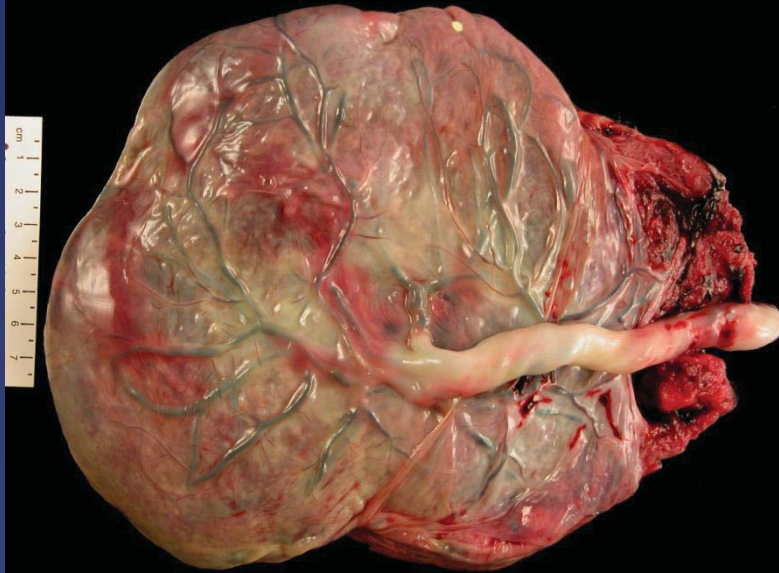


Placental “Critical Values”

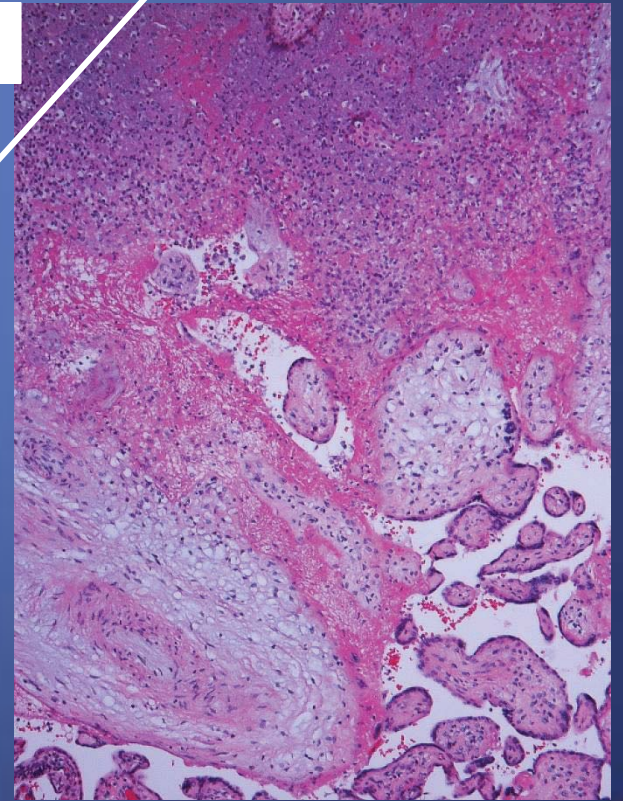
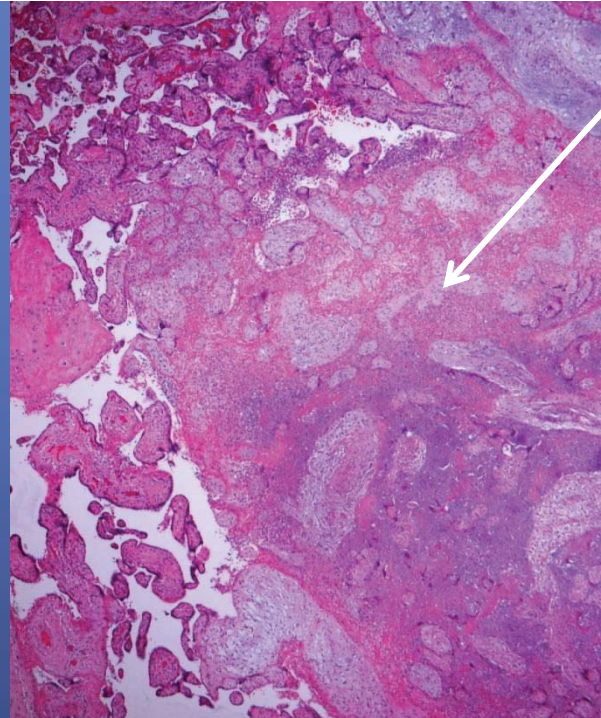
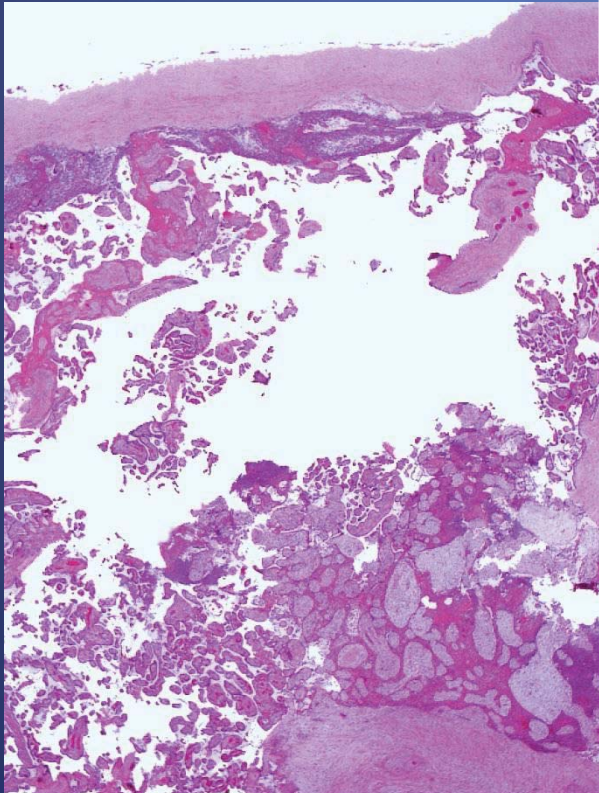
Gross Diagnoses:

Candida Funisitis

Listeria Placentitis



Acute necrotizing villitis



Placental “Critical Values”

Gross Diagnoses:

Candida Funisitis

Listeria Placentitis

Microscopic Diagnoses:

Other Specific Infections: Herpes, CMV, Parvovirus, Toxoplasmosis, Syphilis, Malaria, Chagas etc.

Chorionamnionitis with Grade 2 Fetal Inflammatory Response or Non-occlusive chorionic thrombi

Placental “Critical Values”

Microscopic Diagnoses:

Diffuse High Grade Chronic Villitis and VUE with
Obliterative Vascular Changes

High Grade Fetal Vascular Malperfusion

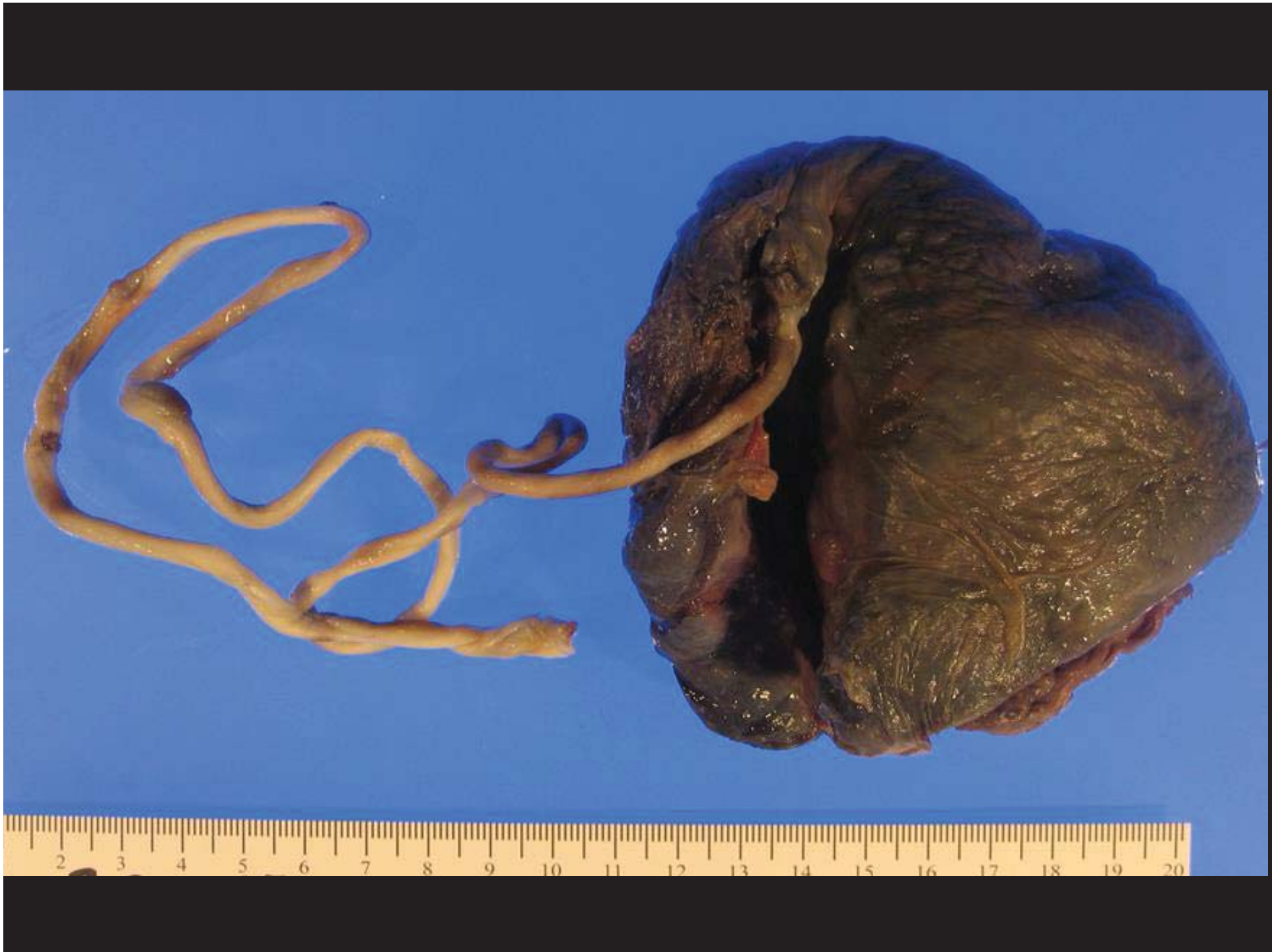
Massive Perivillous Fibrinoid Deposition/Maternal
Floor Infarction

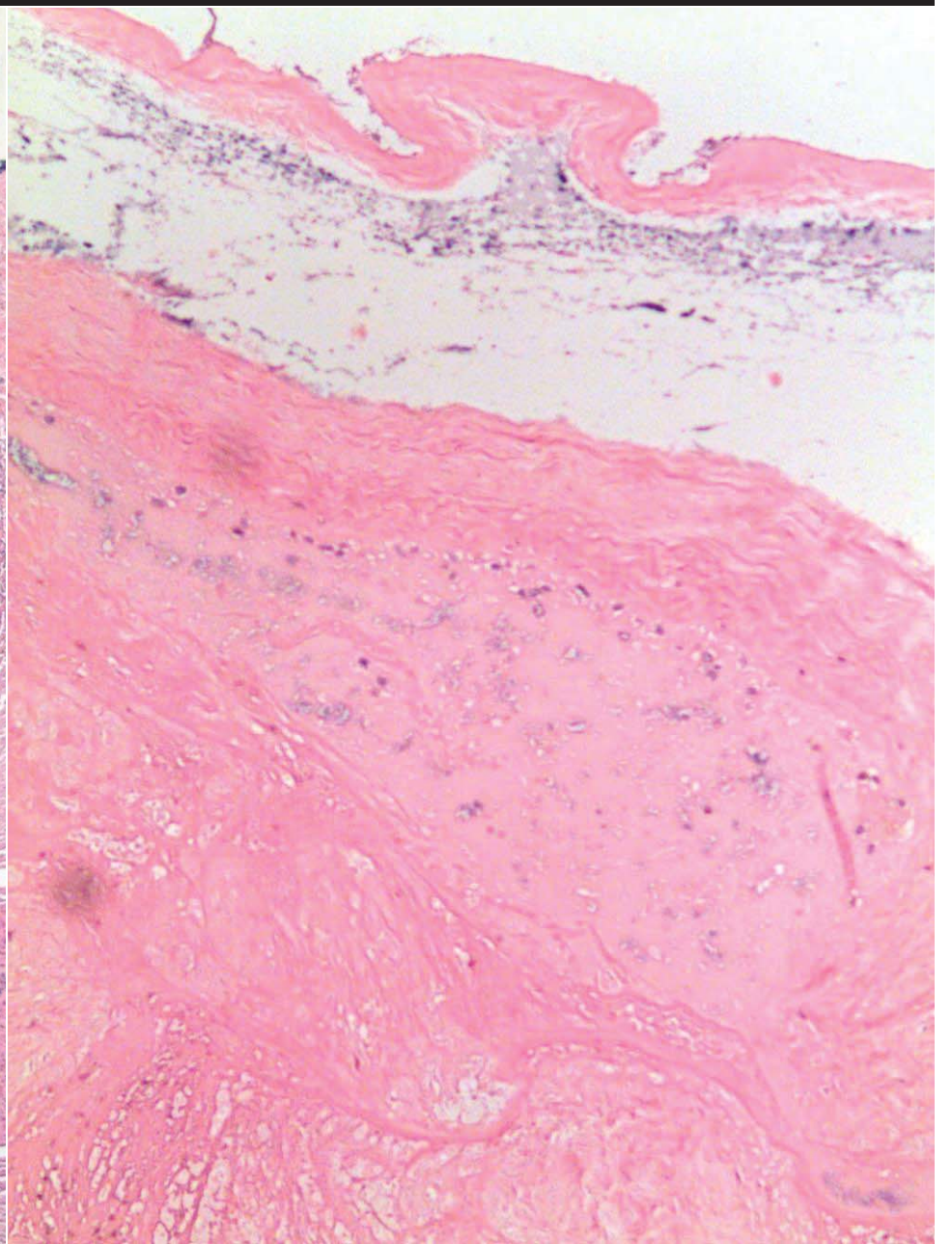
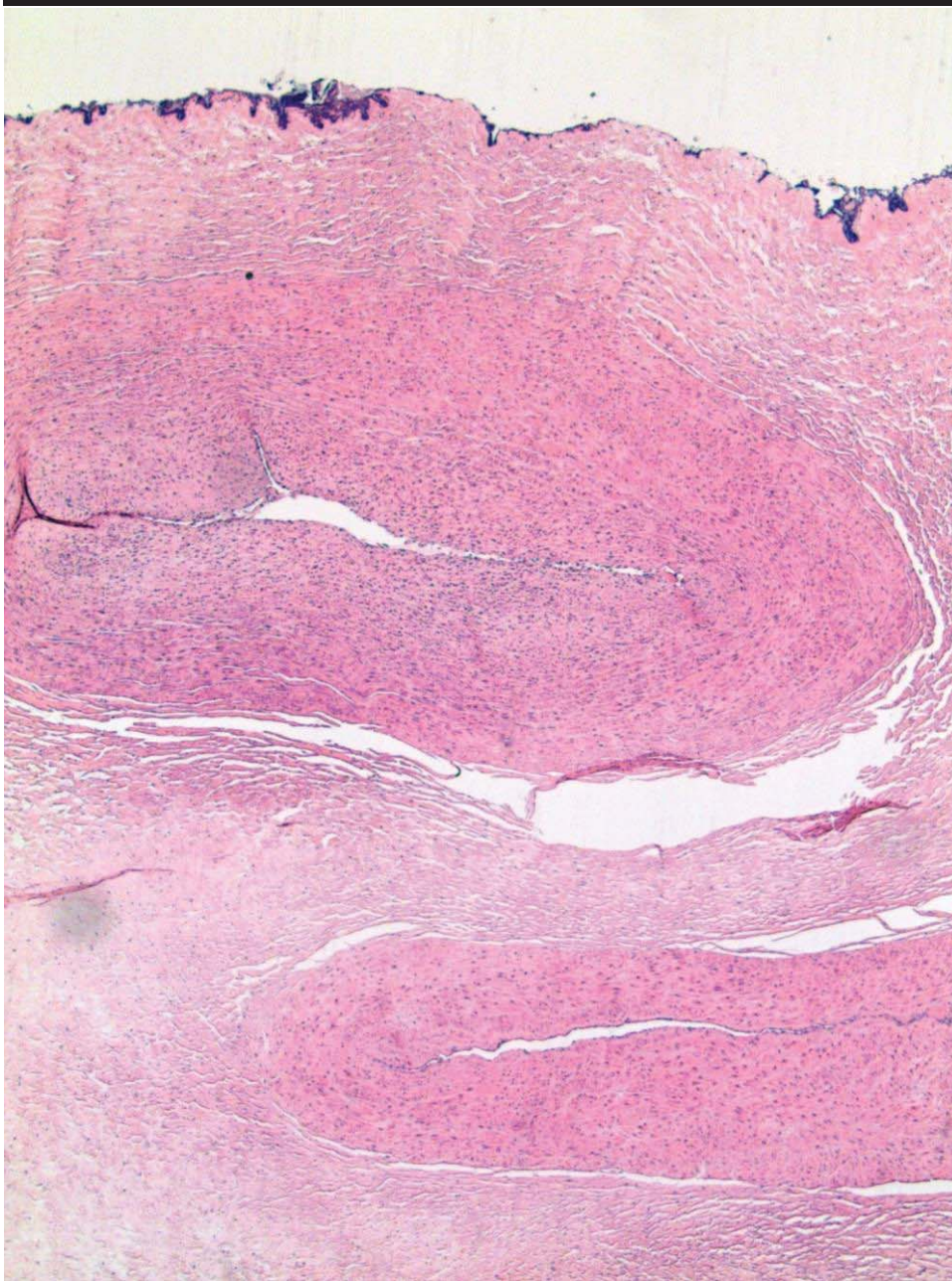
Large Chorangioma

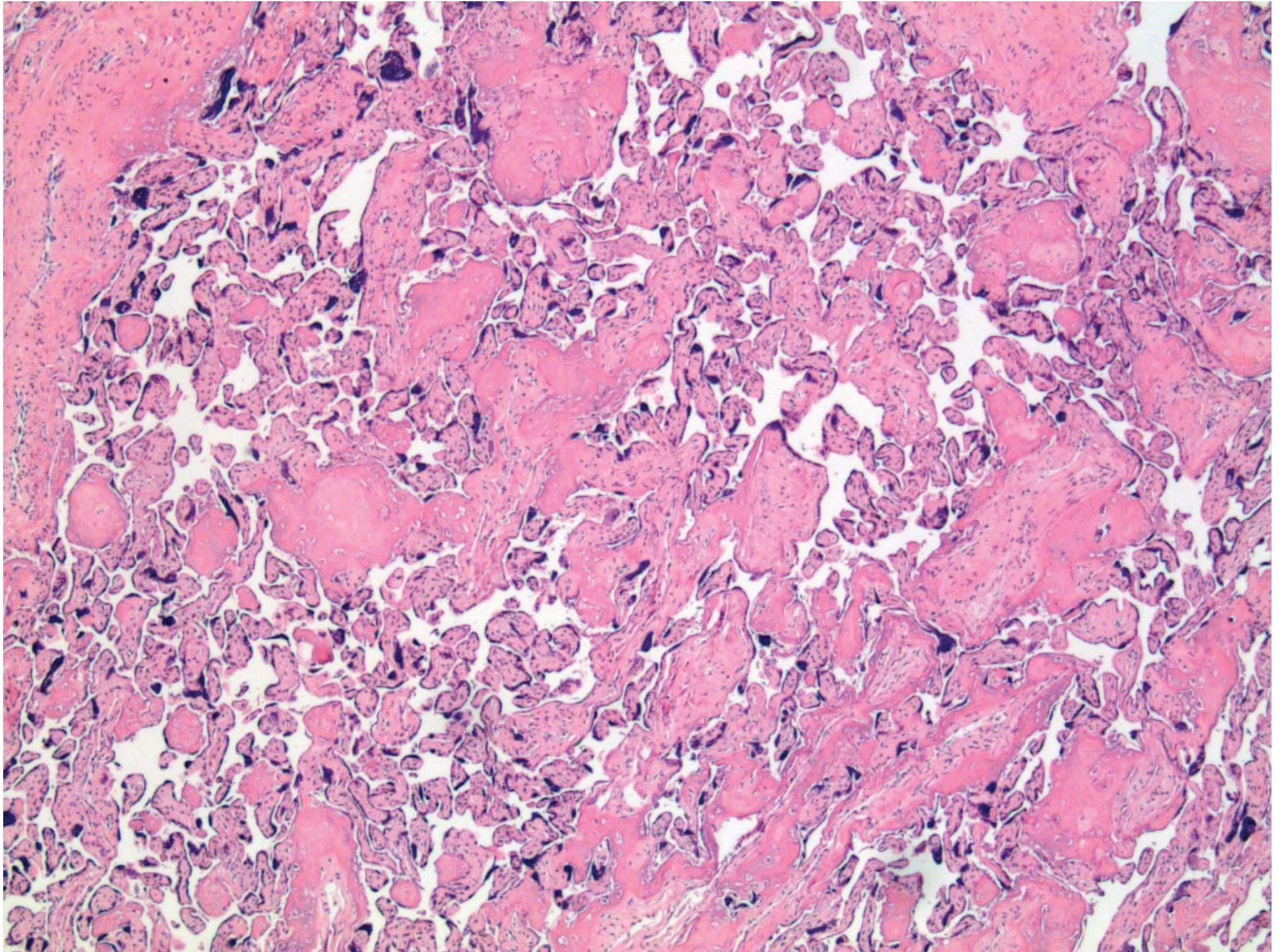
Lotus Delivery Placenta

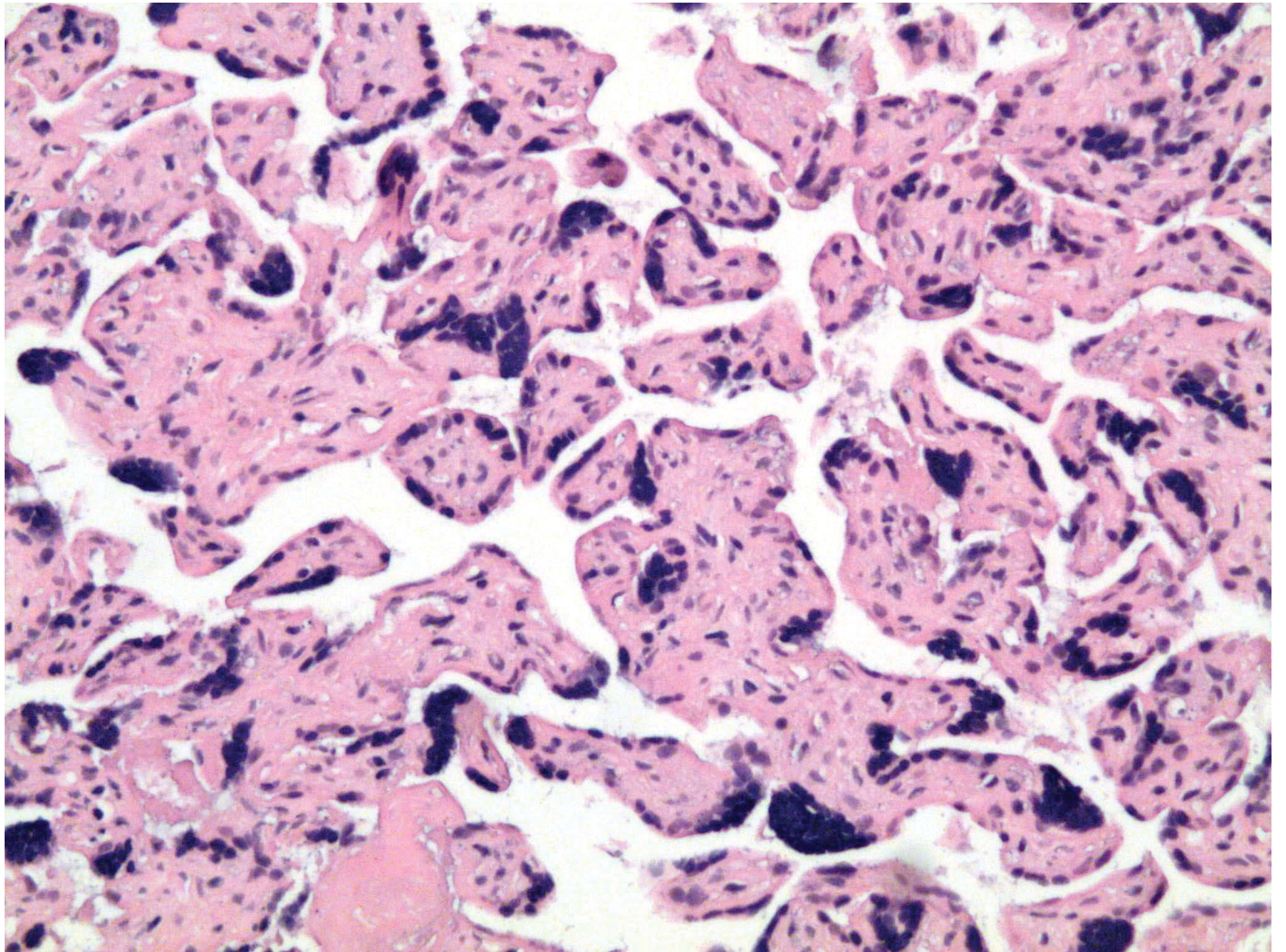
- Male infant born at home at 38 weeks gestation
- Planned non-severance of the umbilical cord
- Birth weight 2664 grams (7th percentile)
- Presented at two days of age with *S. epidermidis* sepsis, hypothermia, and hypoglycemic seizures
- 145 gram placenta (< 3rd percentile)
- Fetal:Placental ratio 18.3 (> 97th percentile)
- Hypocoiled, 0.5 cm diameter, peripherally inserted umbilical cord, single umbilical artery

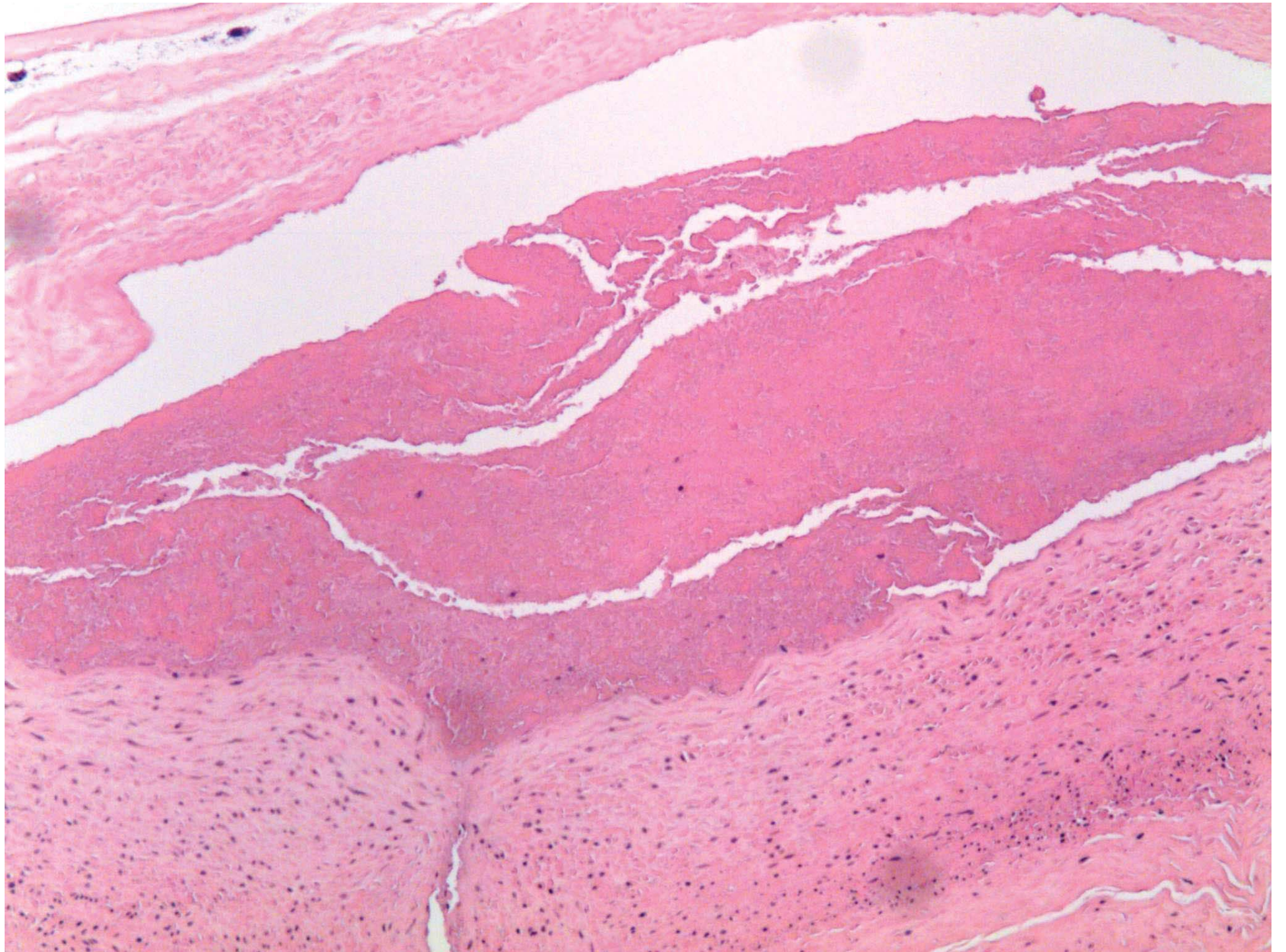












What Happens When a Placenta Works Right?



Thank You