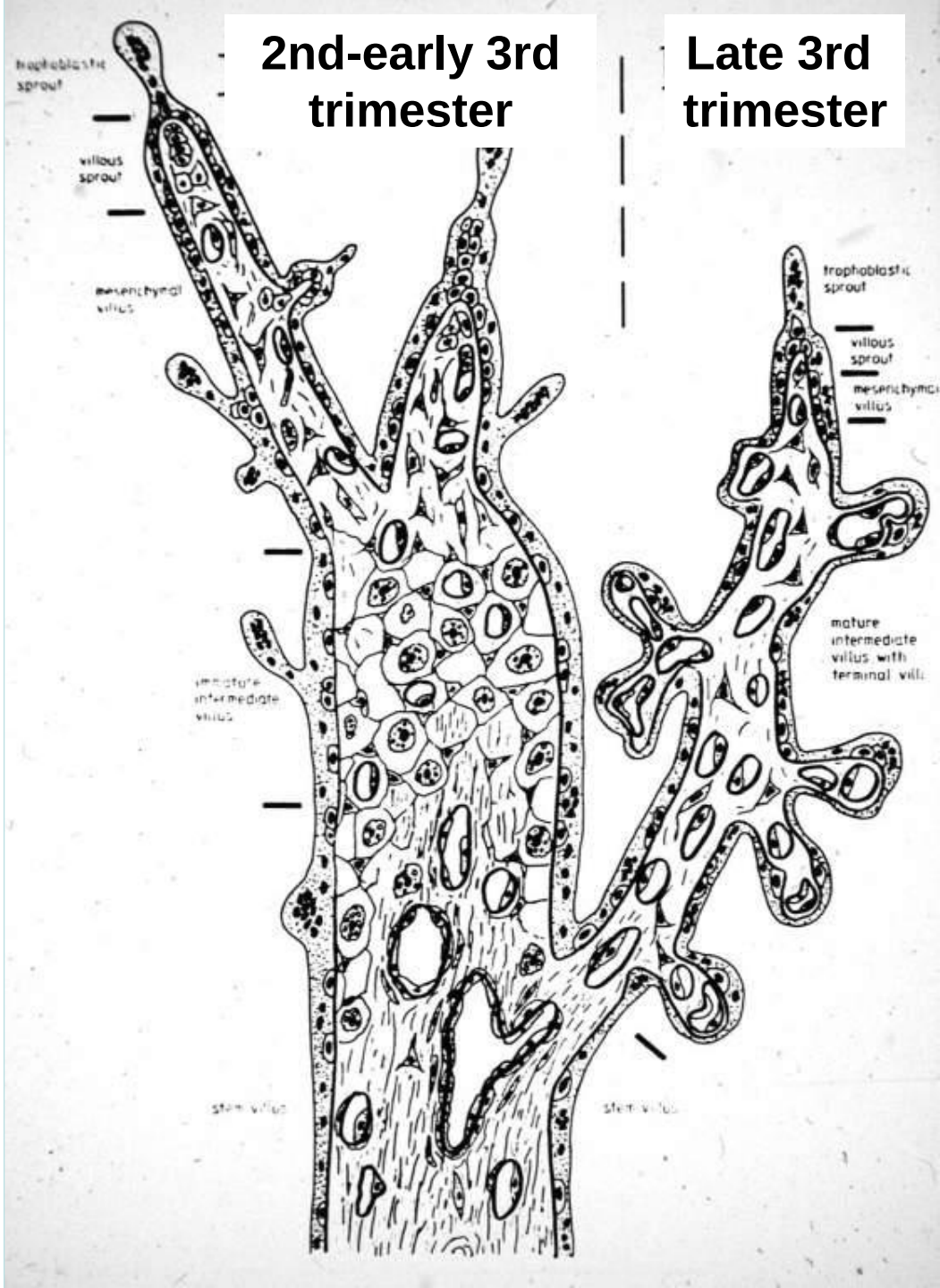
Placental architecture: maturity, vascular pattern, and dysmorphic features

Raymond W Redline, MD
University Hospitals Cleveland Medical Center
Case Western Reserve School of Medicine
Cleveland, OH

Fetal stromal vascular development: normal proximal and distal villi by trimester

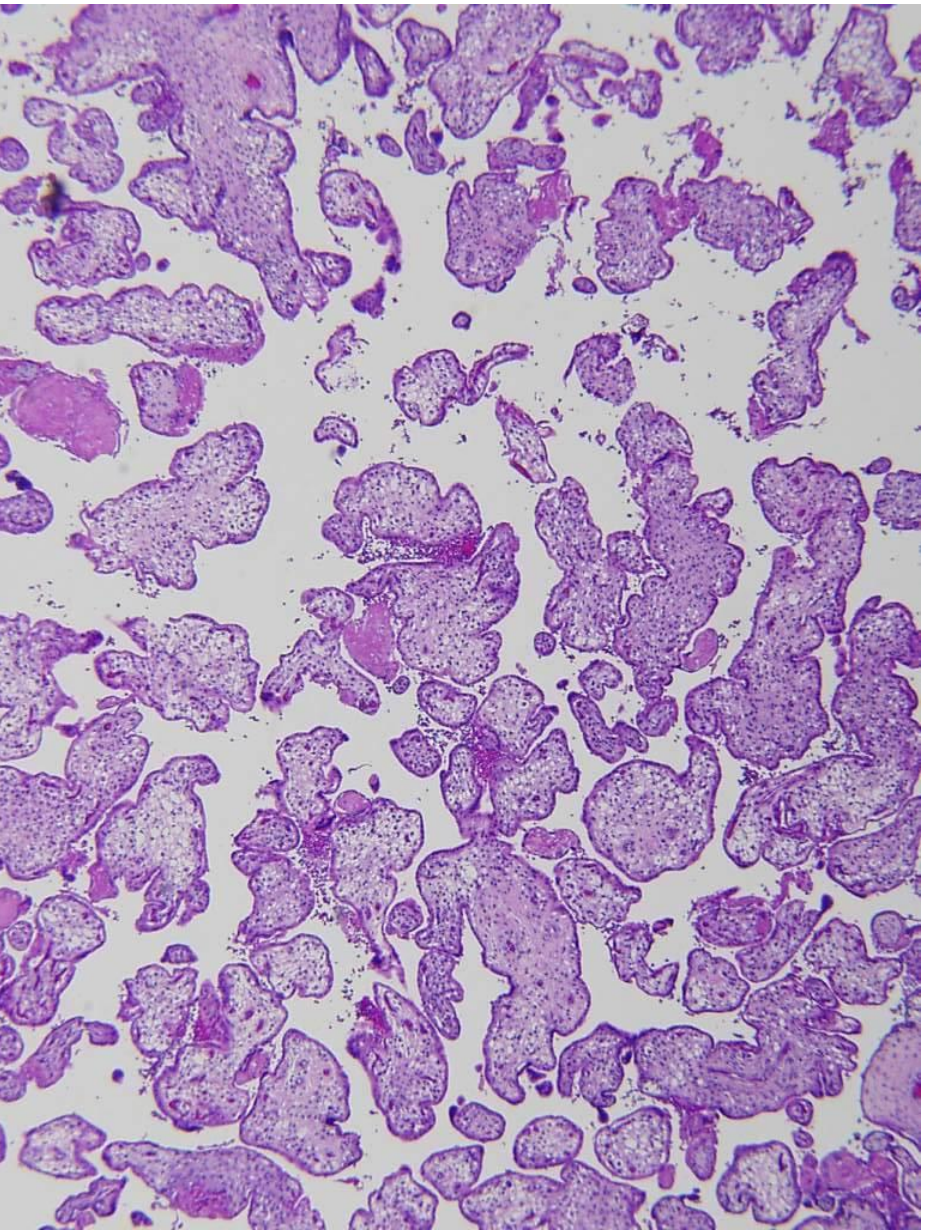
Maternal regulation:
--spiral artery perfusion
--oxygen tension
--nutrient supply

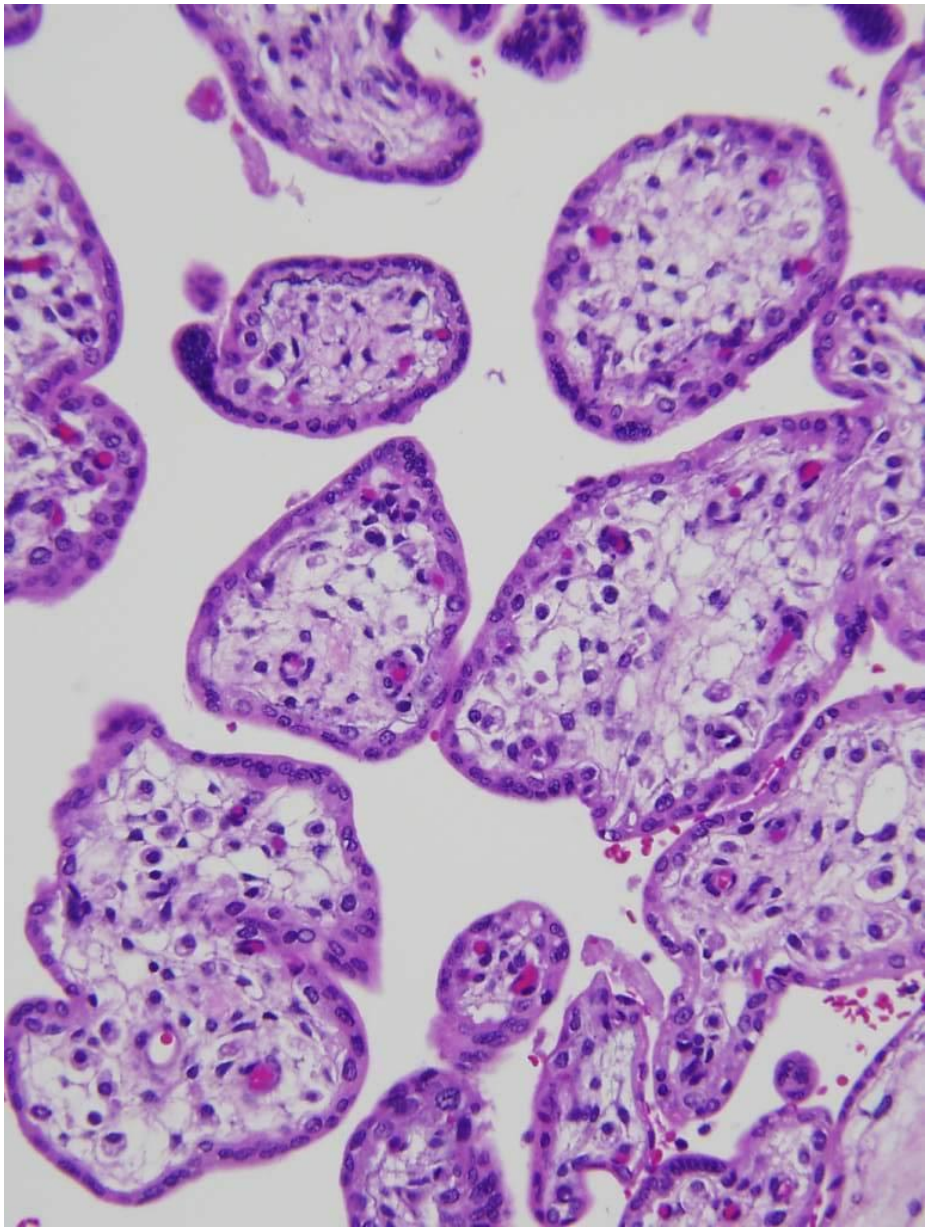
Fetal regulation:
--umbilical perfusion
--growth factor supply
--genetic background



Normal placental maturation patterns for gestational age

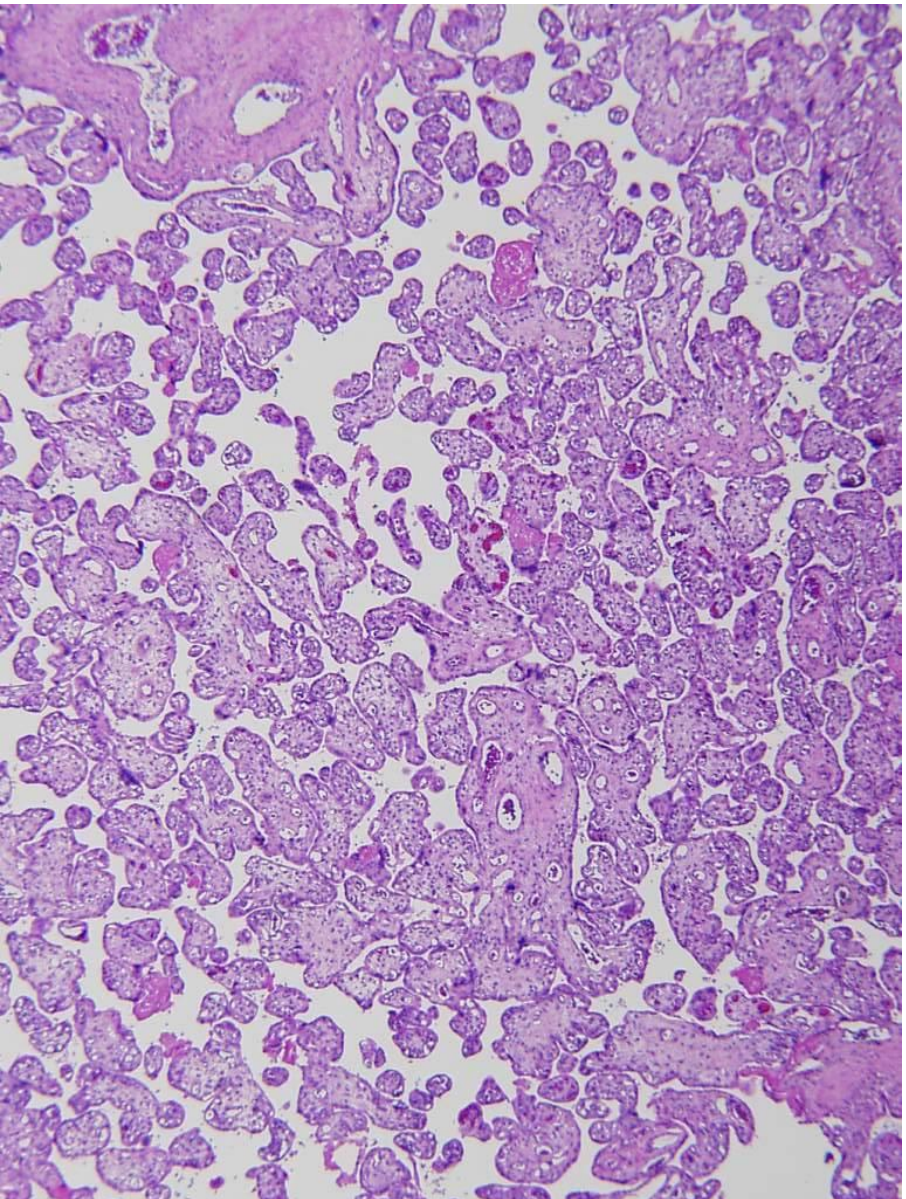
Second trimester 20-23 wks

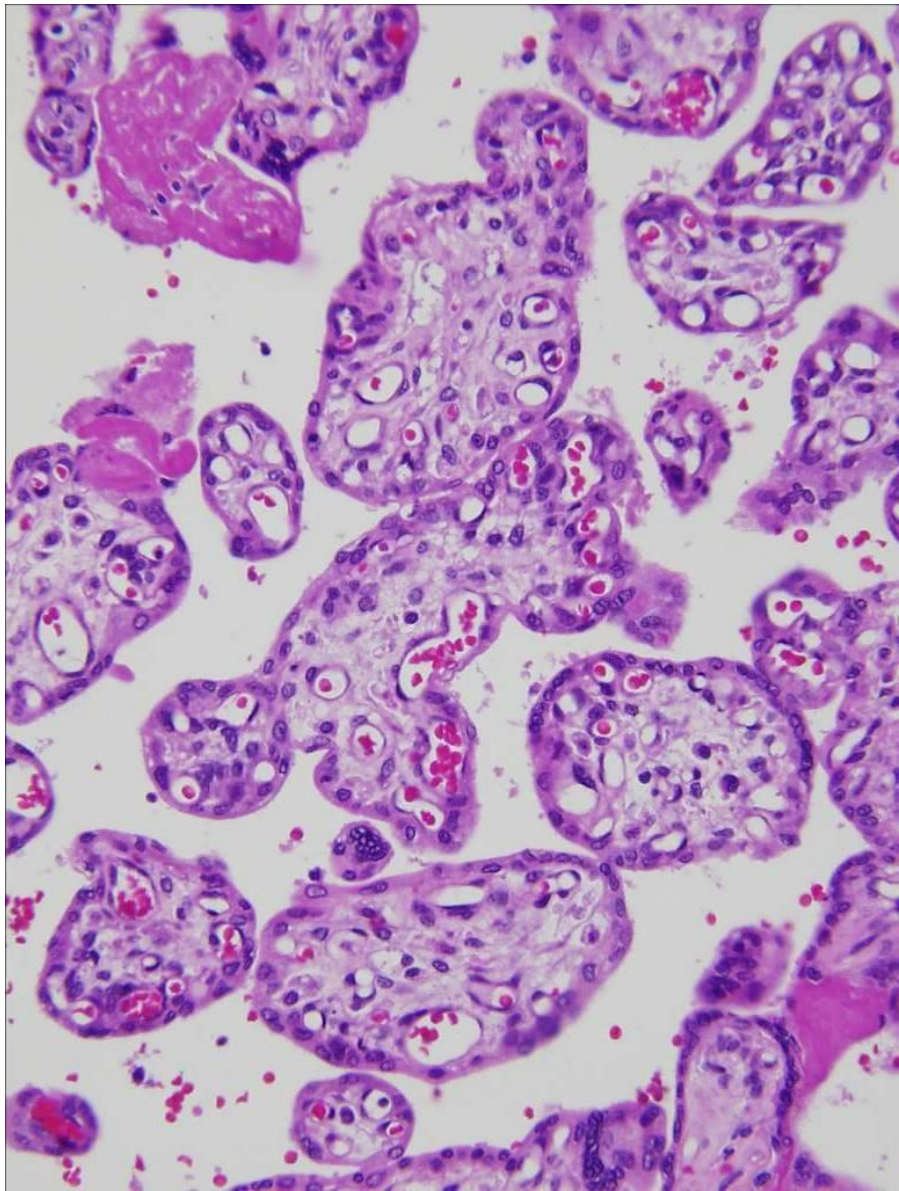




Normal placental maturation patterns for gestational age

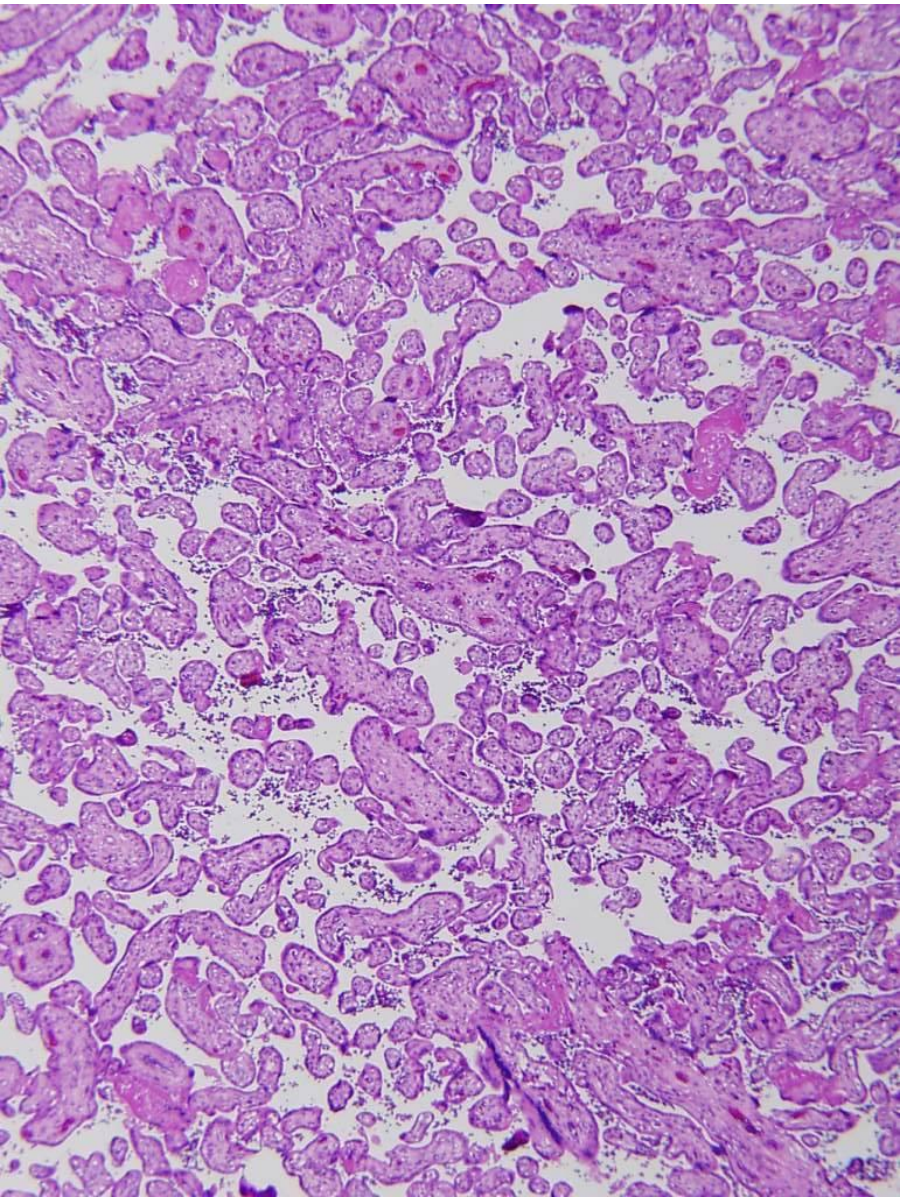
Immature 24-32 wks

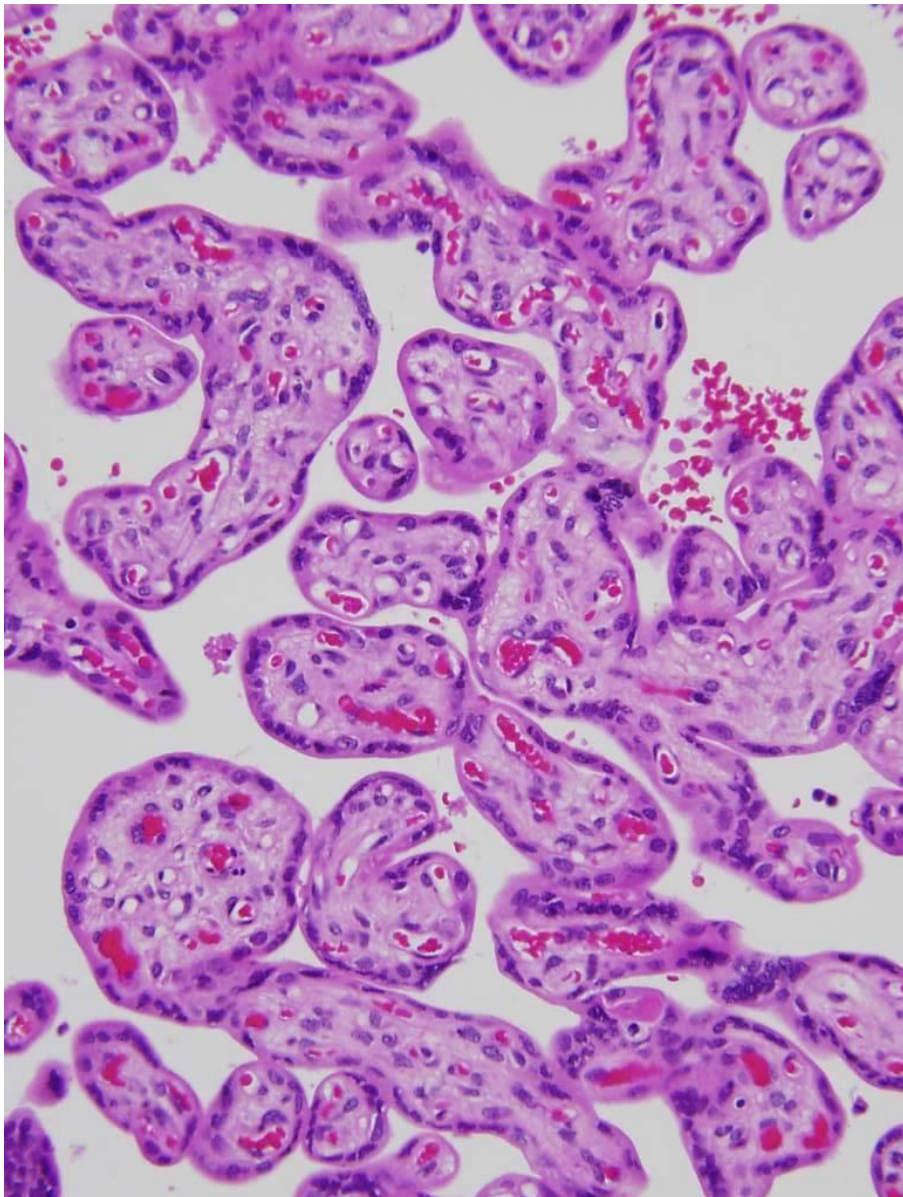




Normal placental maturation patterns for gestational age

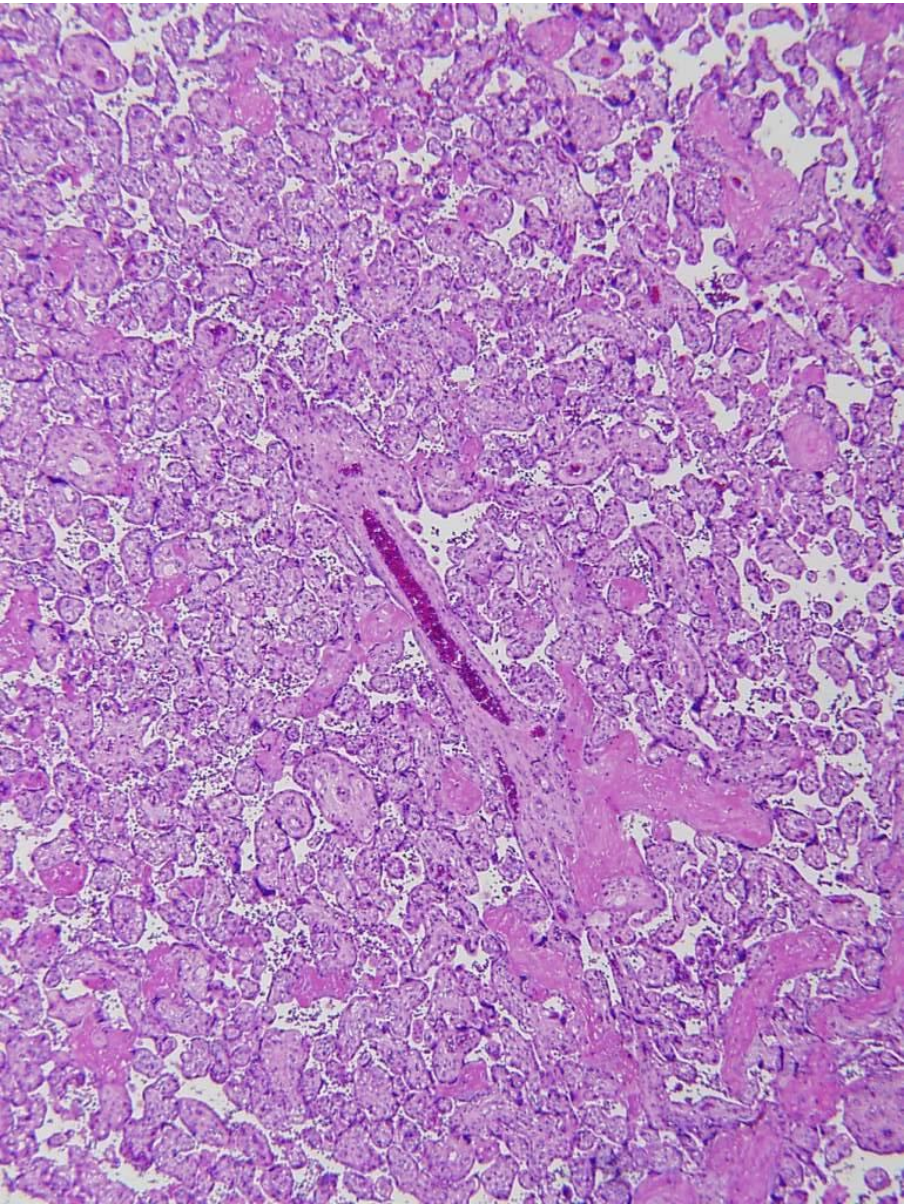
Slightly immature 33-37 weeks

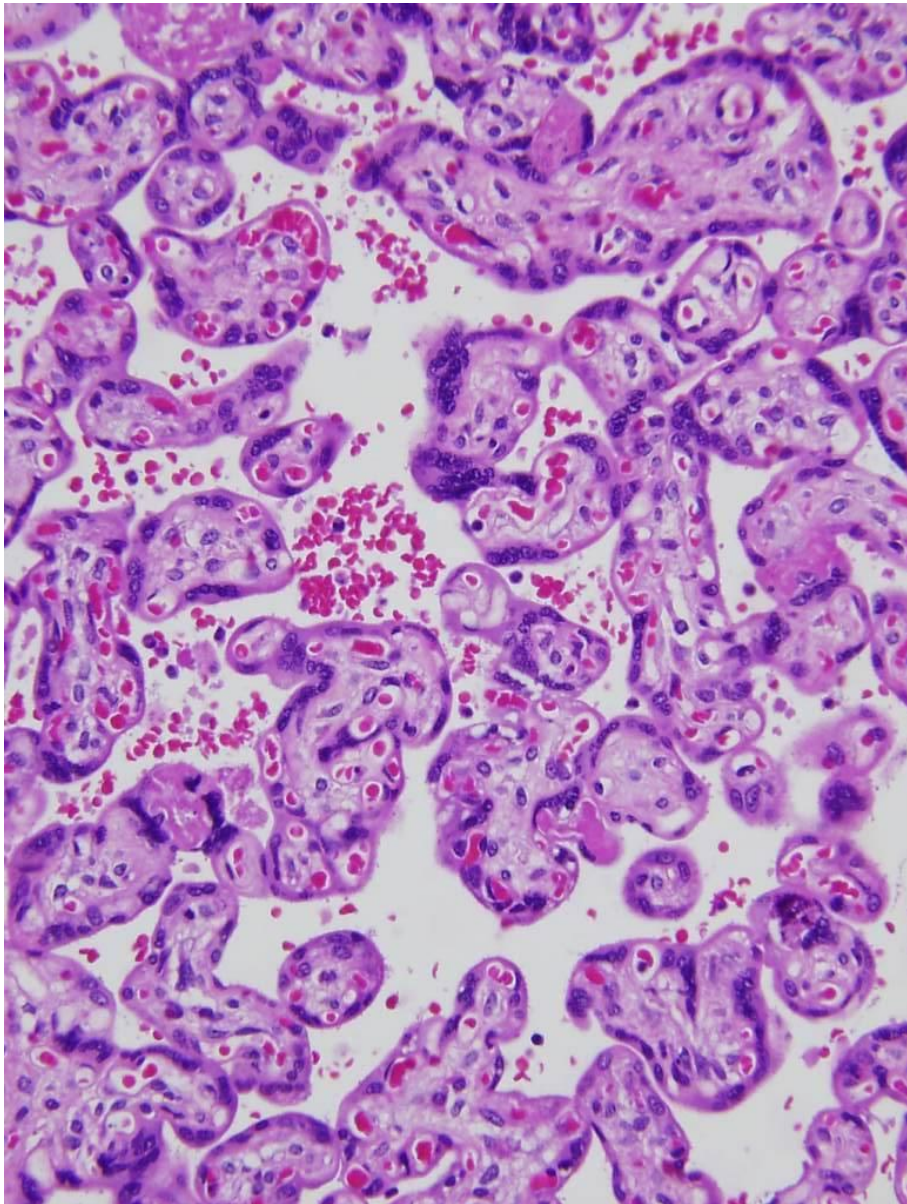




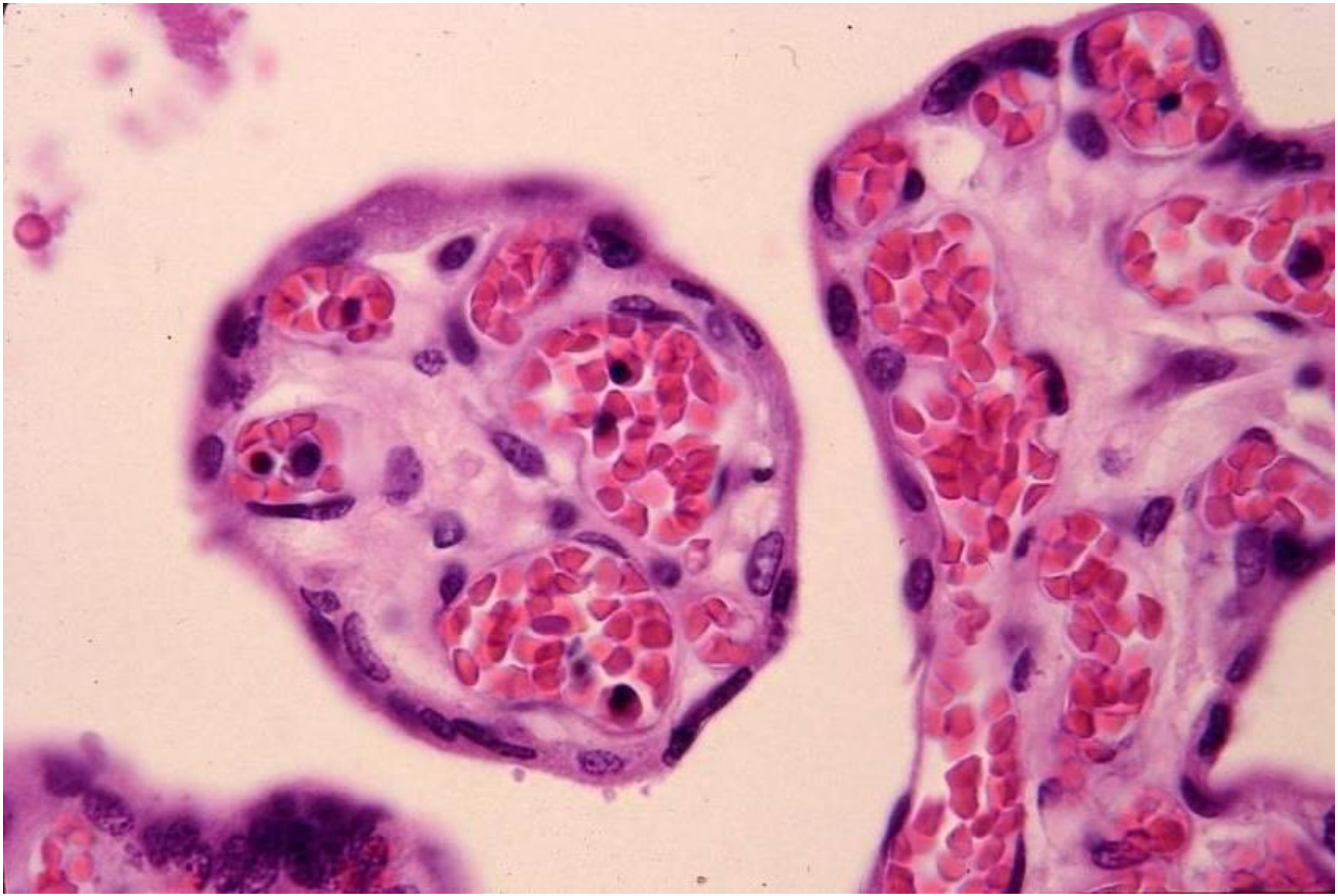
Normal placental maturation patterns for gestational age

Mature > 37 weeks





Normal vasculo-syncytial membranes



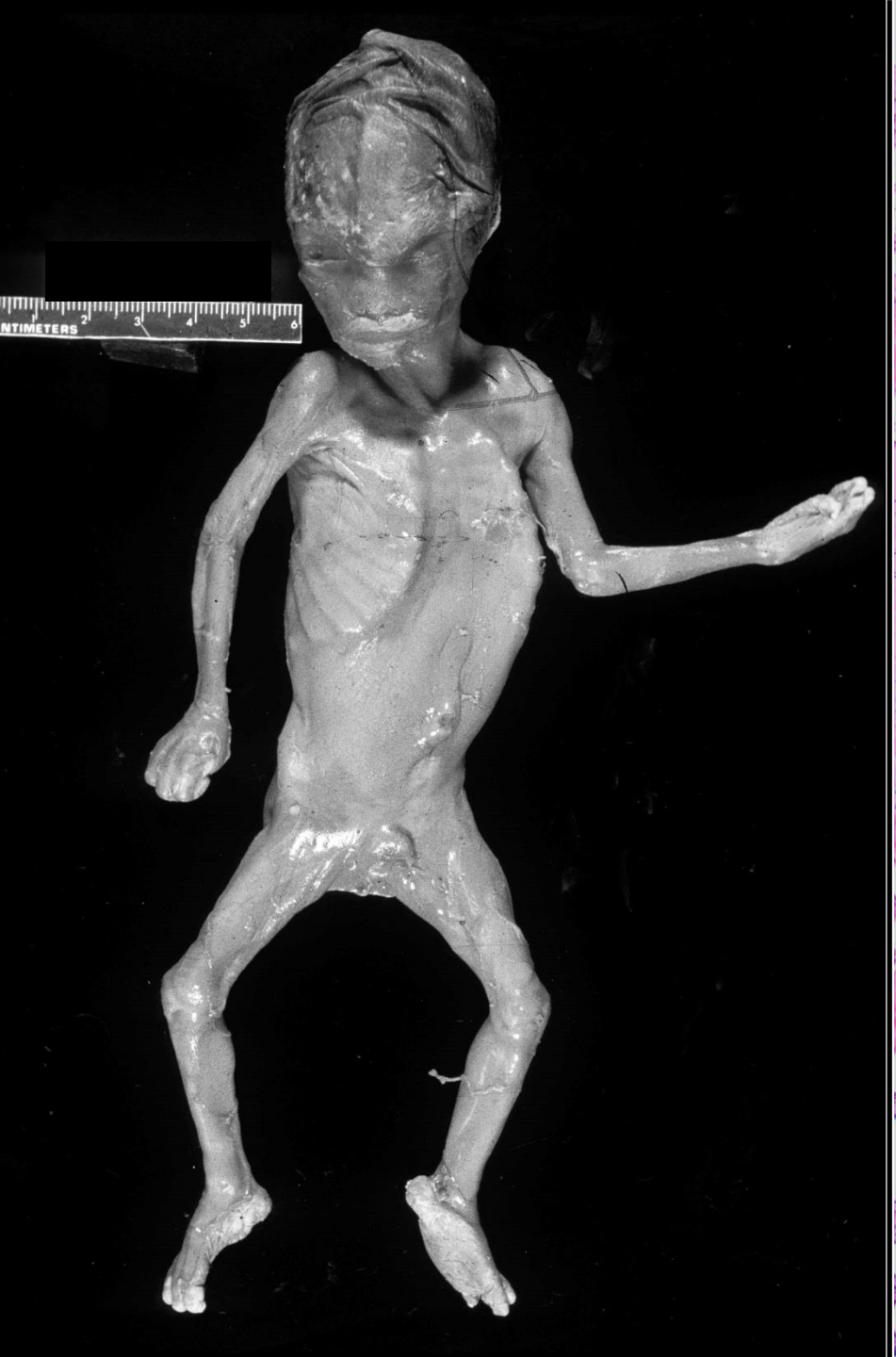
Maturity for gestational age

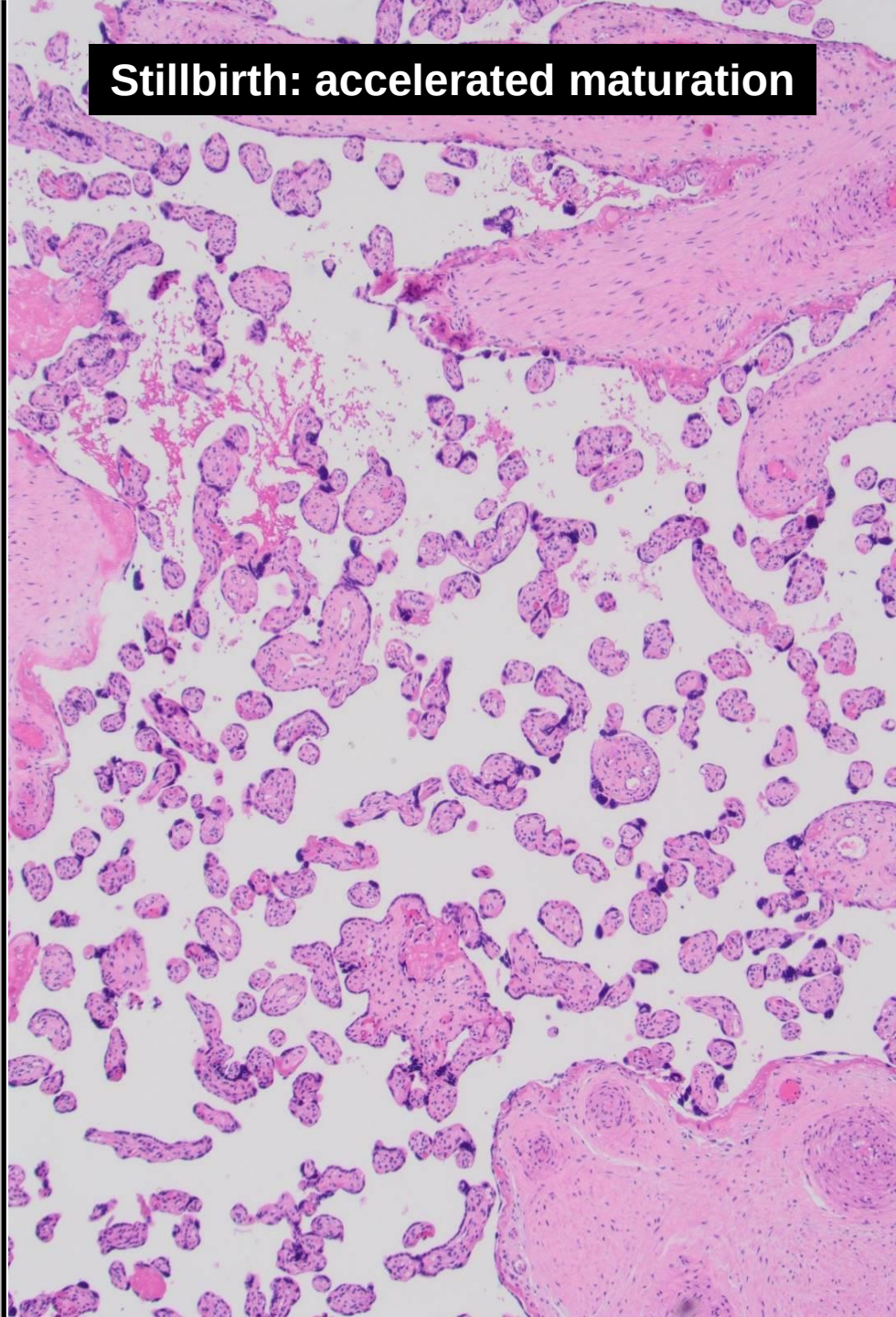
- Immature = <32 wk pattern at <37 wks
- Slightly immature = 32-37 wk pattern, any GA
- Mature = >37 wk pattern at >32 wks

Histologically mature =
"mature-like" pattern at <32 wks

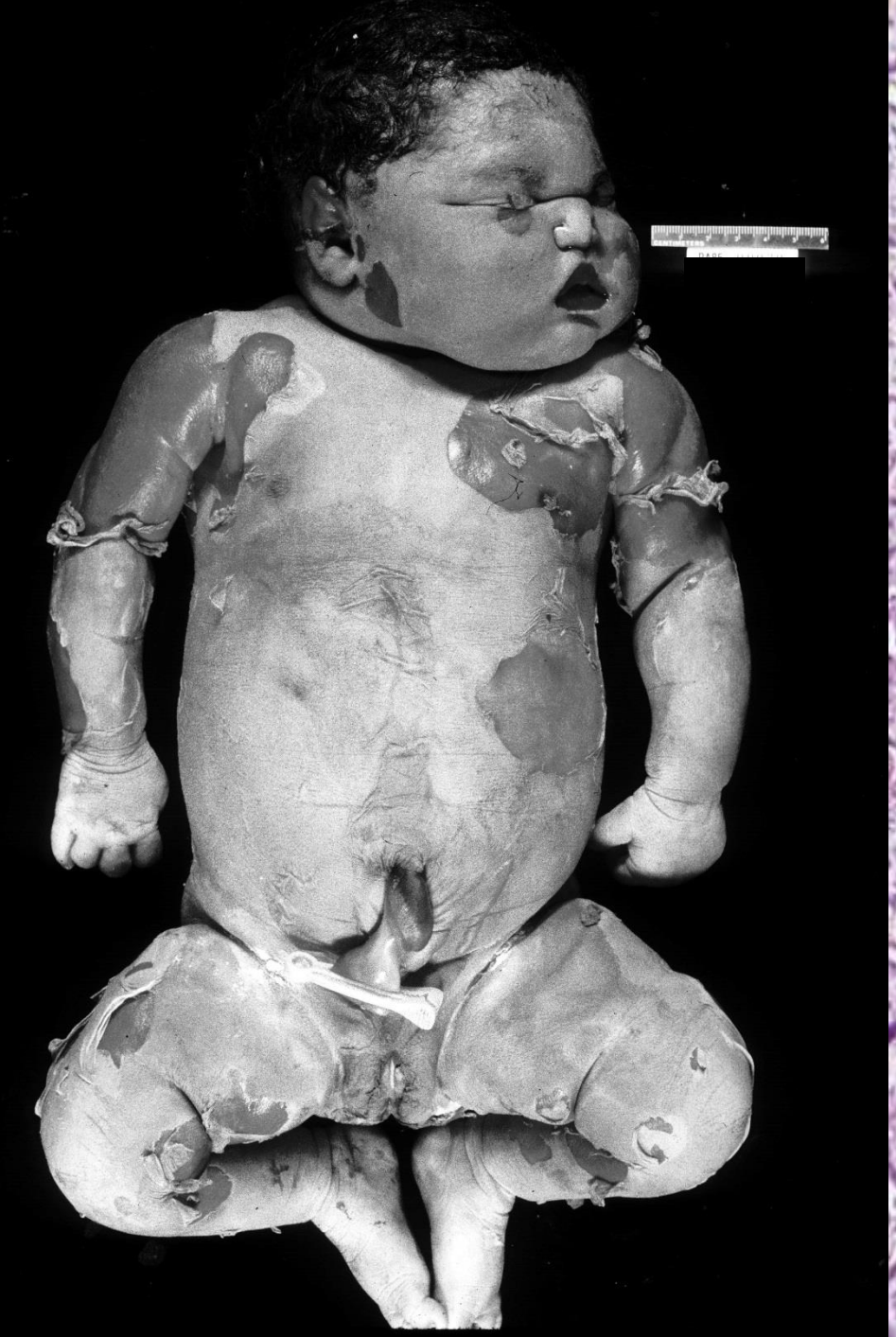
Histologically immature =
"immature-like" pattern at >37 wks

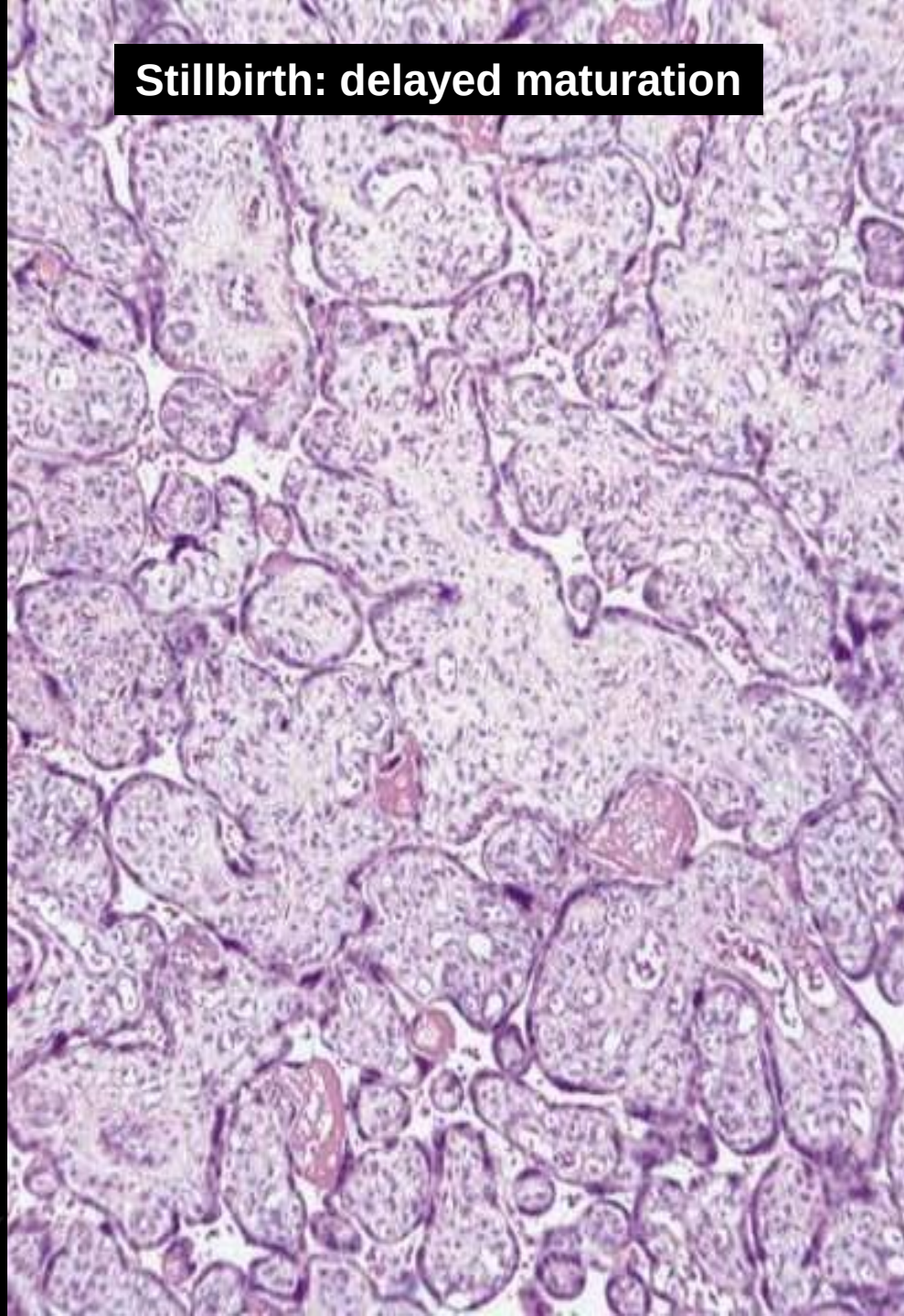
Redline, Diagnostic Histopathology 2012; 18(5):189-94
Redline et al, Mod Pathol 2021, doi.org/10.1038/s41379-021-00747-4





Stillbirth: accelerated maturation





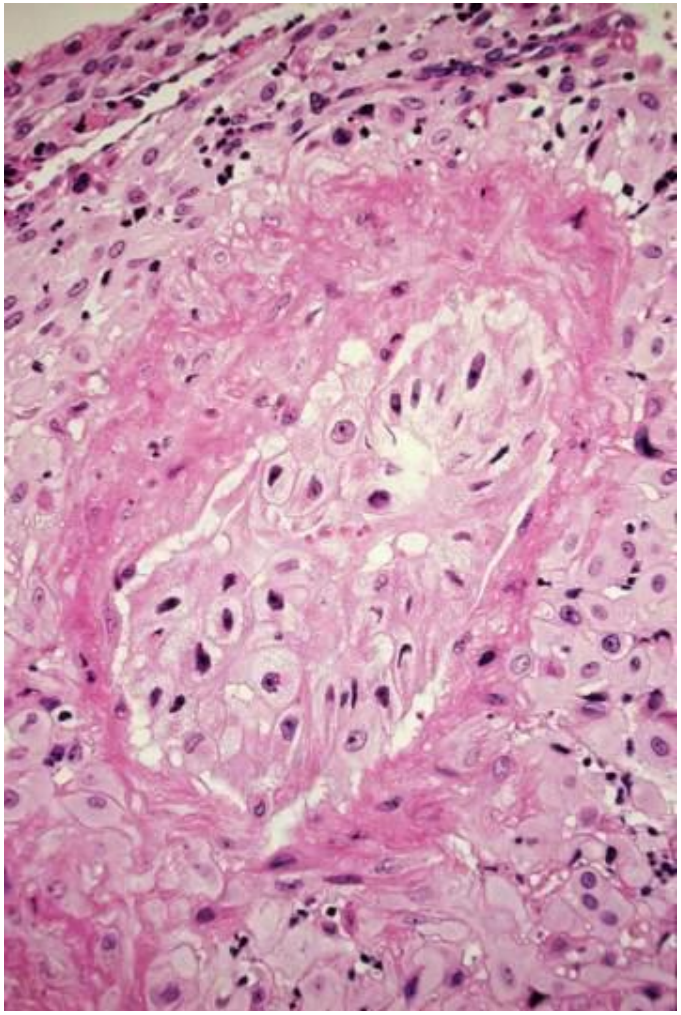
Stillbirth: delayed maturation

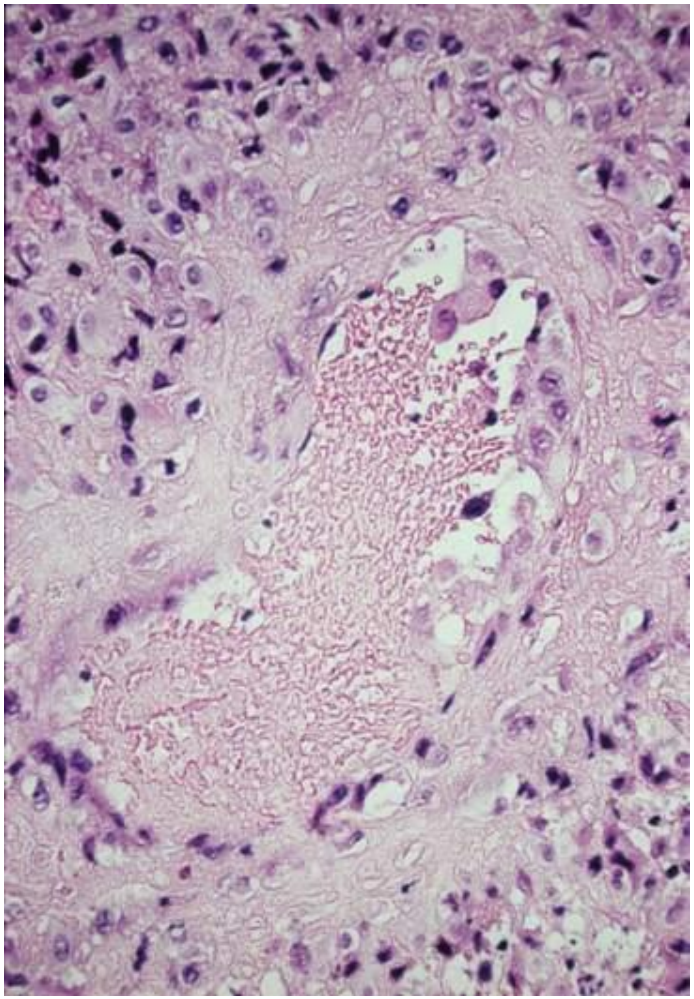
Categories of Placental Pathology

Maternal vascular lesions:

1. Maldevelopment:
    - Defective arterial remodeling
    - Superficial implantation
2. Malperfusion:
    - Partial:
        - Accelerated villous maturation
        - Distal villous hypoplasia
    - Complete: villous infarcts
3. Loss of Integrity:
    - Abruptio placenta
    - Marginal separation

Normal spiral arterial remodeling

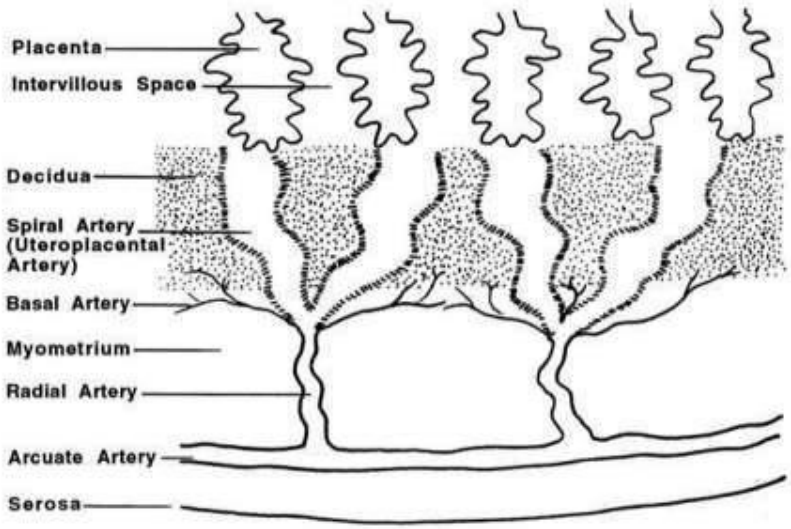


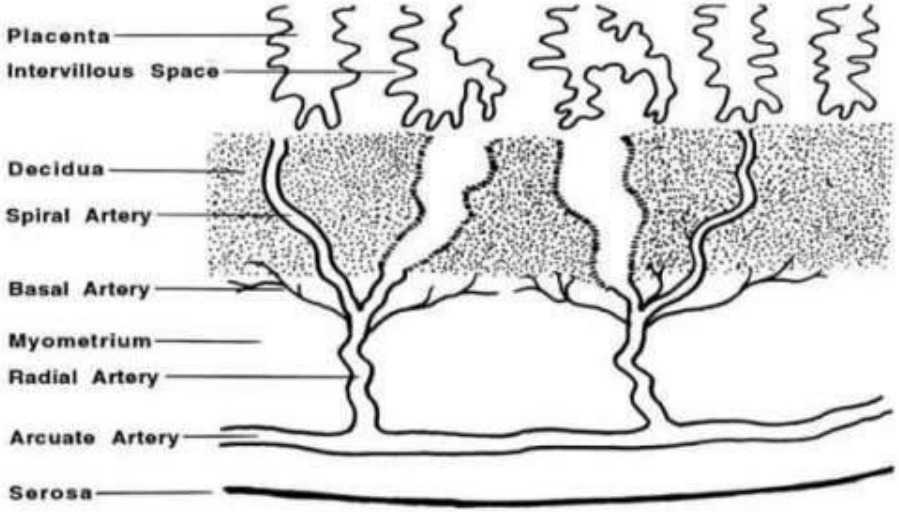


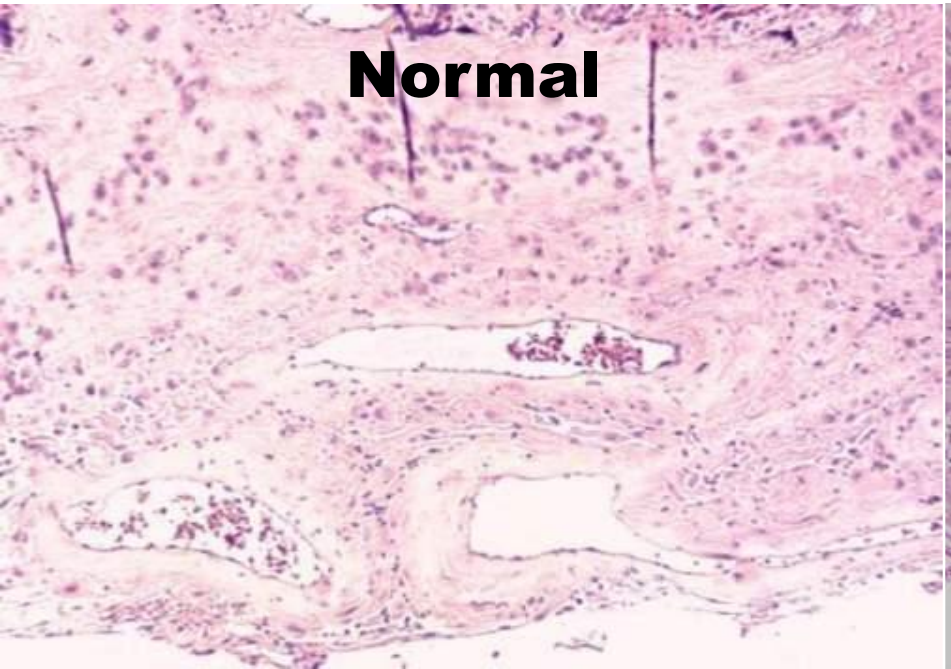
Early: intravascular trophoblast plug

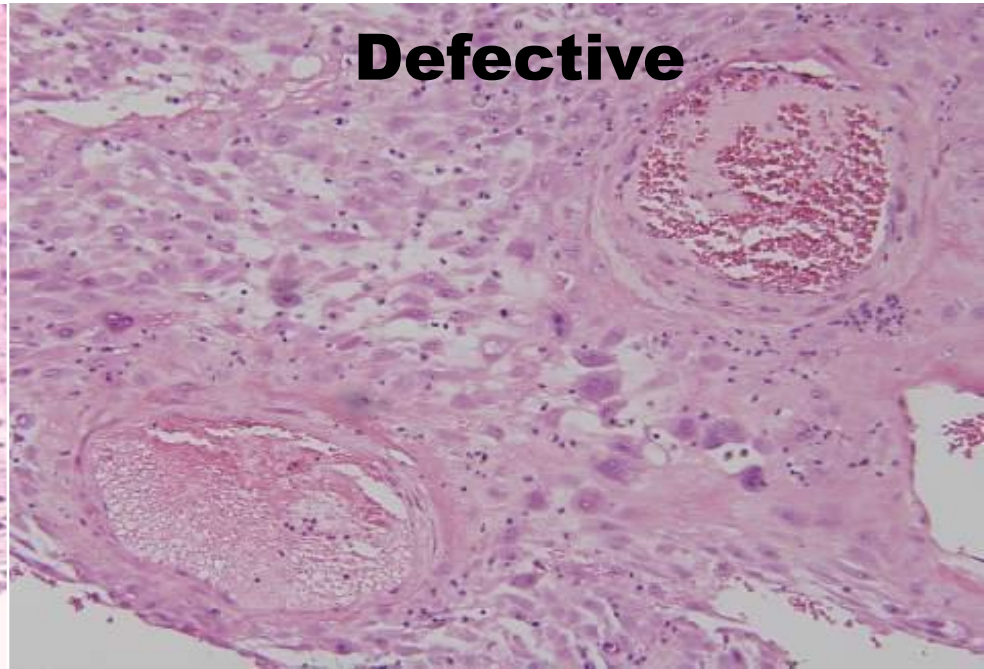
Later: trophoblast remodeling of arterial wall

Maternal vascular maldevelopment: defective arterial remodeling/ superficial implantation

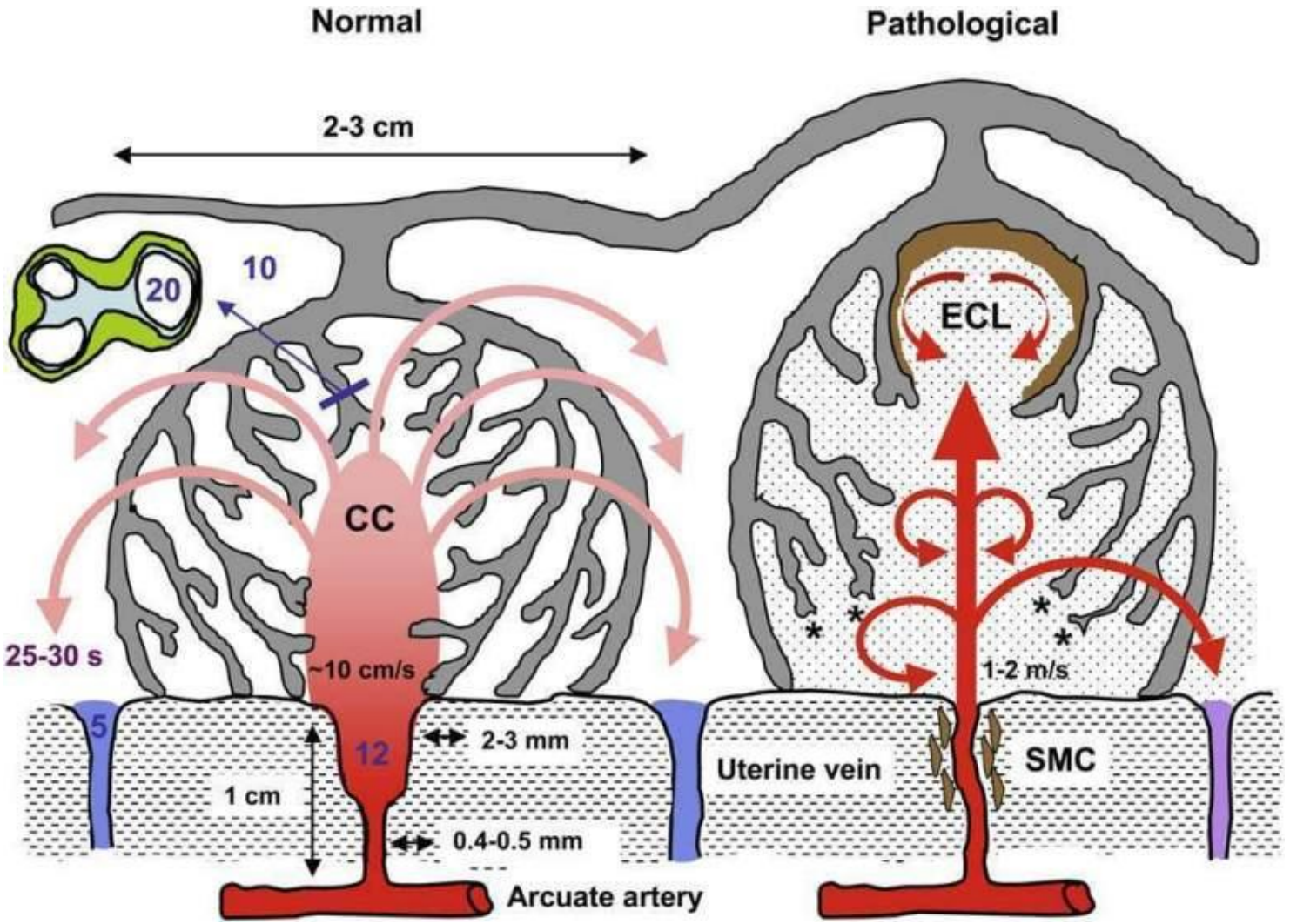








Maternal vascular malperfusion



GJ Burton, Placenta 2009; 30: 473-482

Gross placental findings in maternal vascular malperfusion

↓	Fetal weight for GA
↓↓	Placental weight for GA
↑	Fetoplacental weight ratio
↑	Placental (length–width)
↑↓	Variable placental thickness
↑	Peripheral umbilical cord insertion (<3cm)
↓	Umbilical cord diameter (<0.8cm)

Accelerated villous maturation

= *histologic changes due to oxidative stress induced-senescence in maternal vascular malperfusion*

Pathophysiology

-DNA damage

-Cell cycle arrest

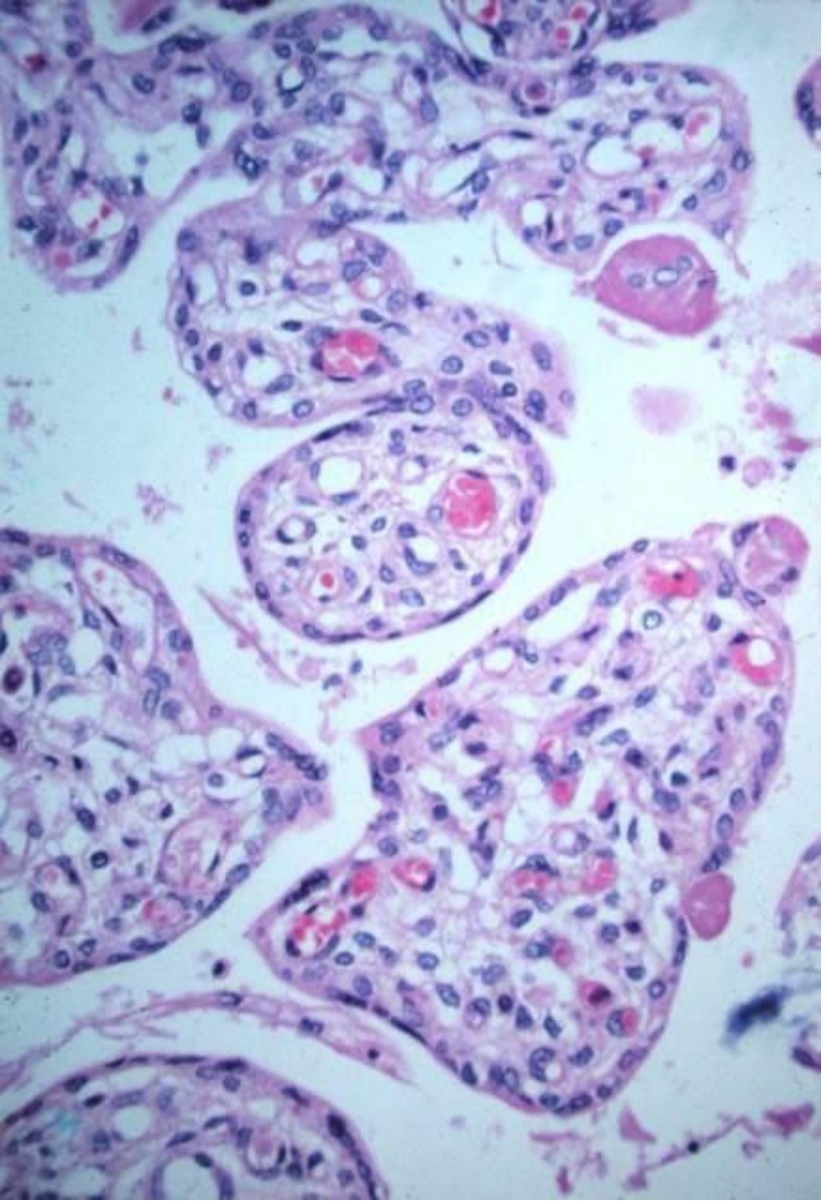
-senescence-associated “secretory phenotype”

Biomarkers

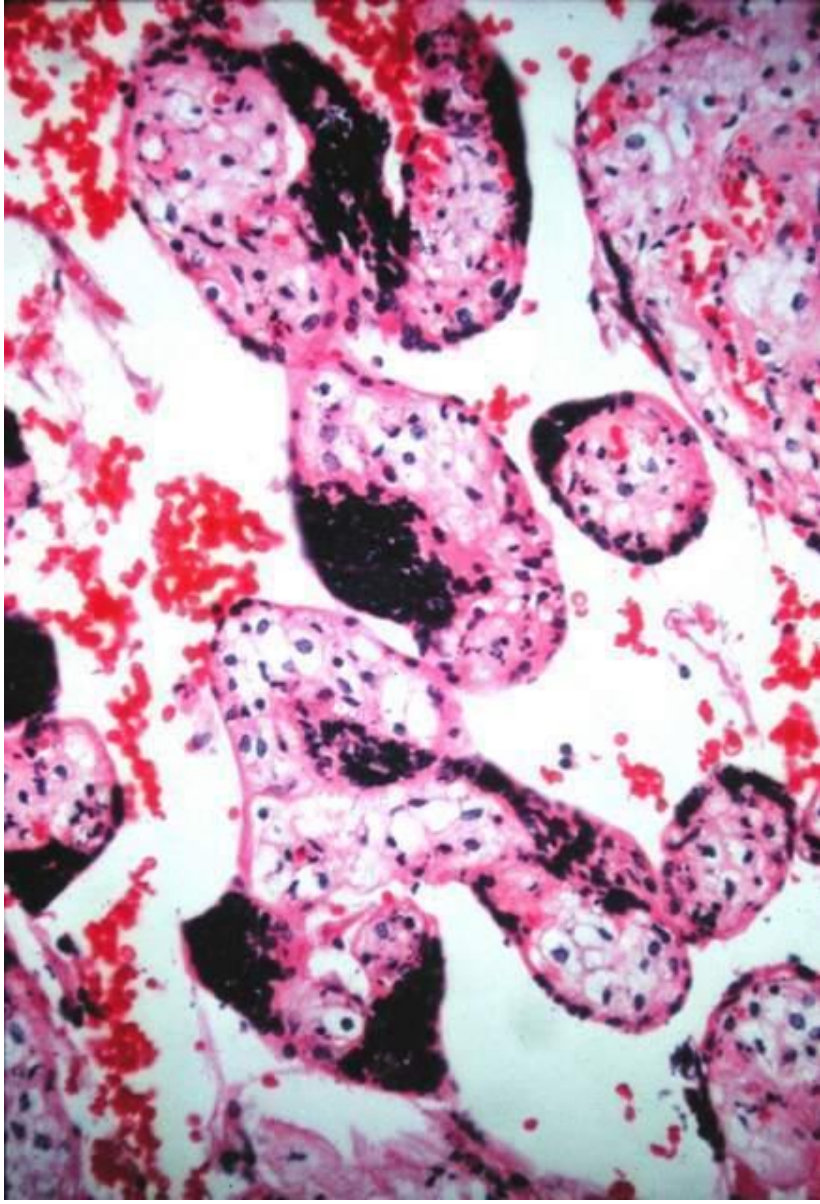
- increased circulating fetal DNA

- anti-endothelial proteins: s-flt (preeclampsia)

GJ Burton, Placenta 2018; 68: 15-22



Oxidative stress



Increased syncytial knots: rate of formation > rate of deportation

Maternal vascular malperfusion
Accelerated villous maturation

Definition:

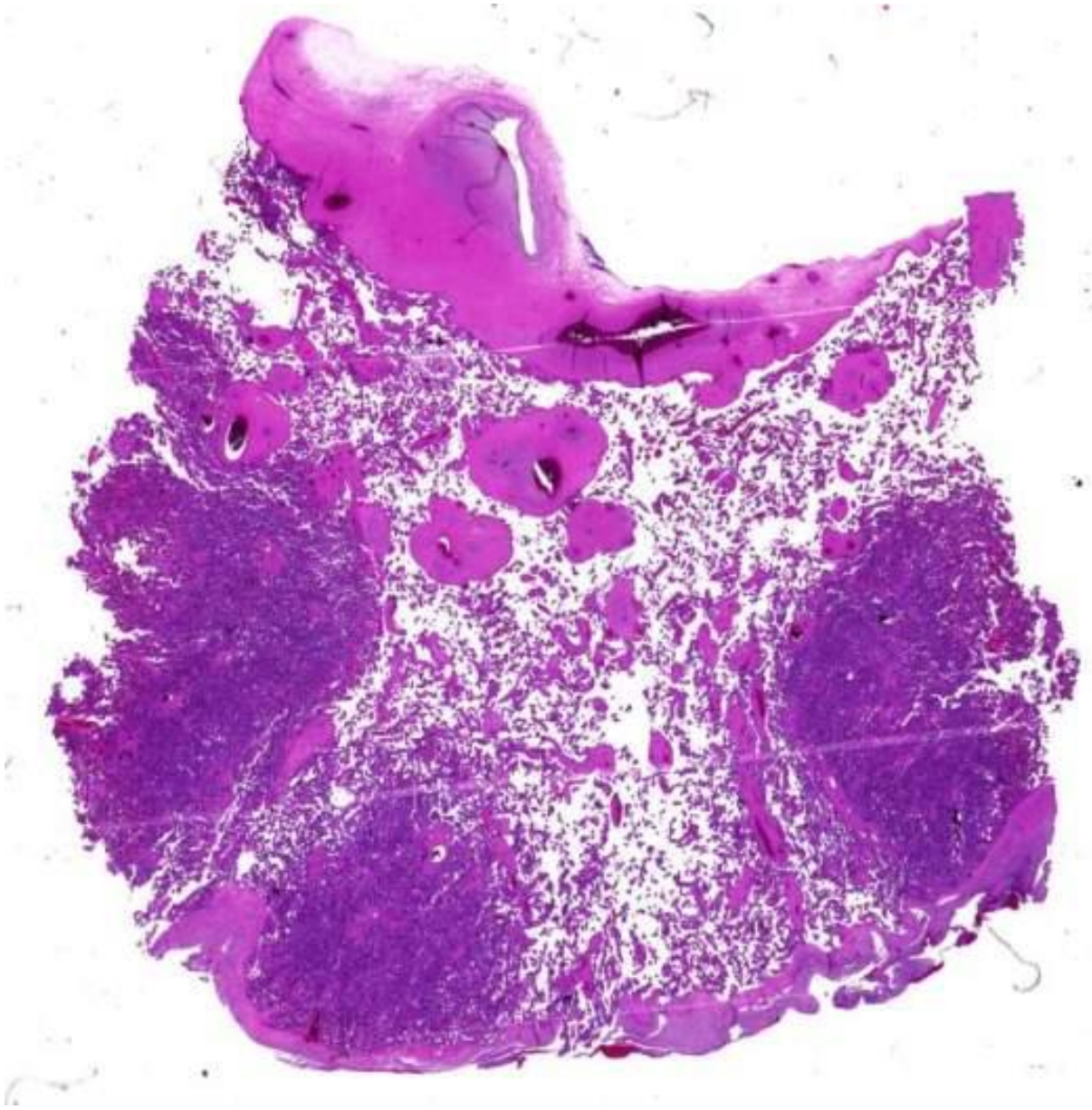
1. Alternating areas of villous crowding and paucity
2. *Crowded areas*: often adjacent to stem villi, large dense syncytial knots, ↑ intervillous fibrin, villous agglutination.
3. *Areas of paucity*: ↑ intervillous space, thin villi with ↓ branching.

Associations: small placenta, ↑ fetoplacental weight ratio, maternal hypertension, fetal growth restriction, decidual arteriopathy

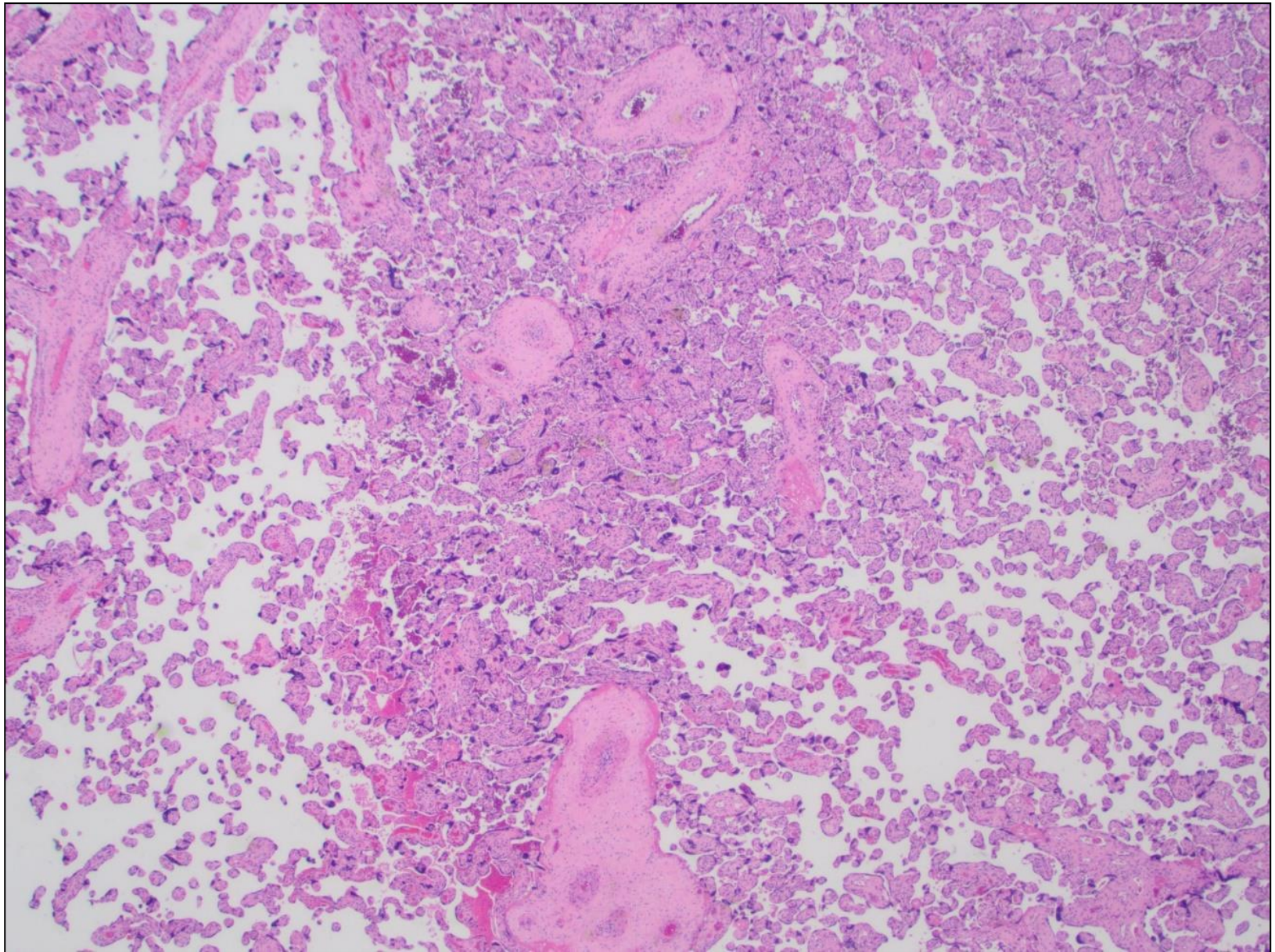
Complications: insufficient maternal oxygen/ nutrient delivery, FGR, spontaneous or indicated preterm delivery

Altered lobular architecture (slide on tray)

alternating areas of crowding and paucity

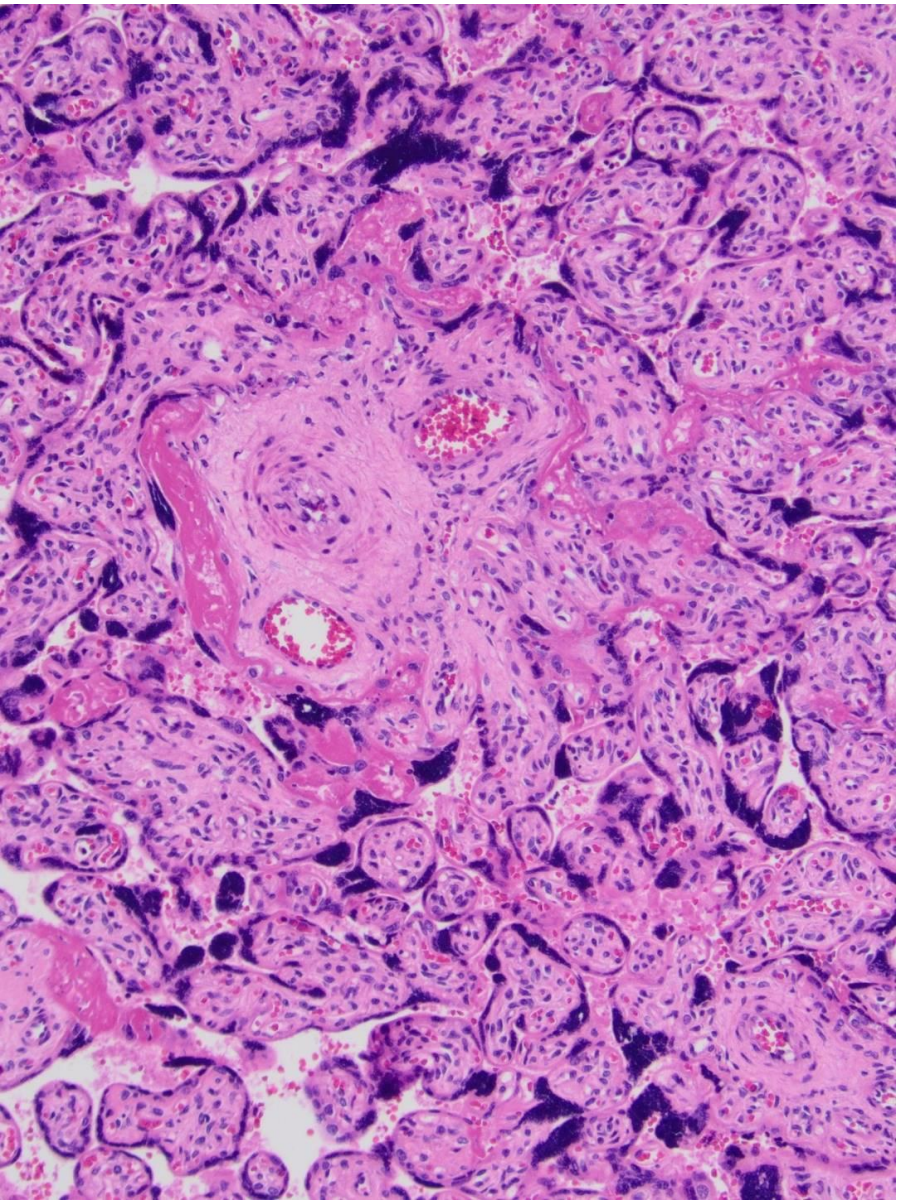


Altered lobular architecture (2X)
(alternating areas of crowding and paucity)

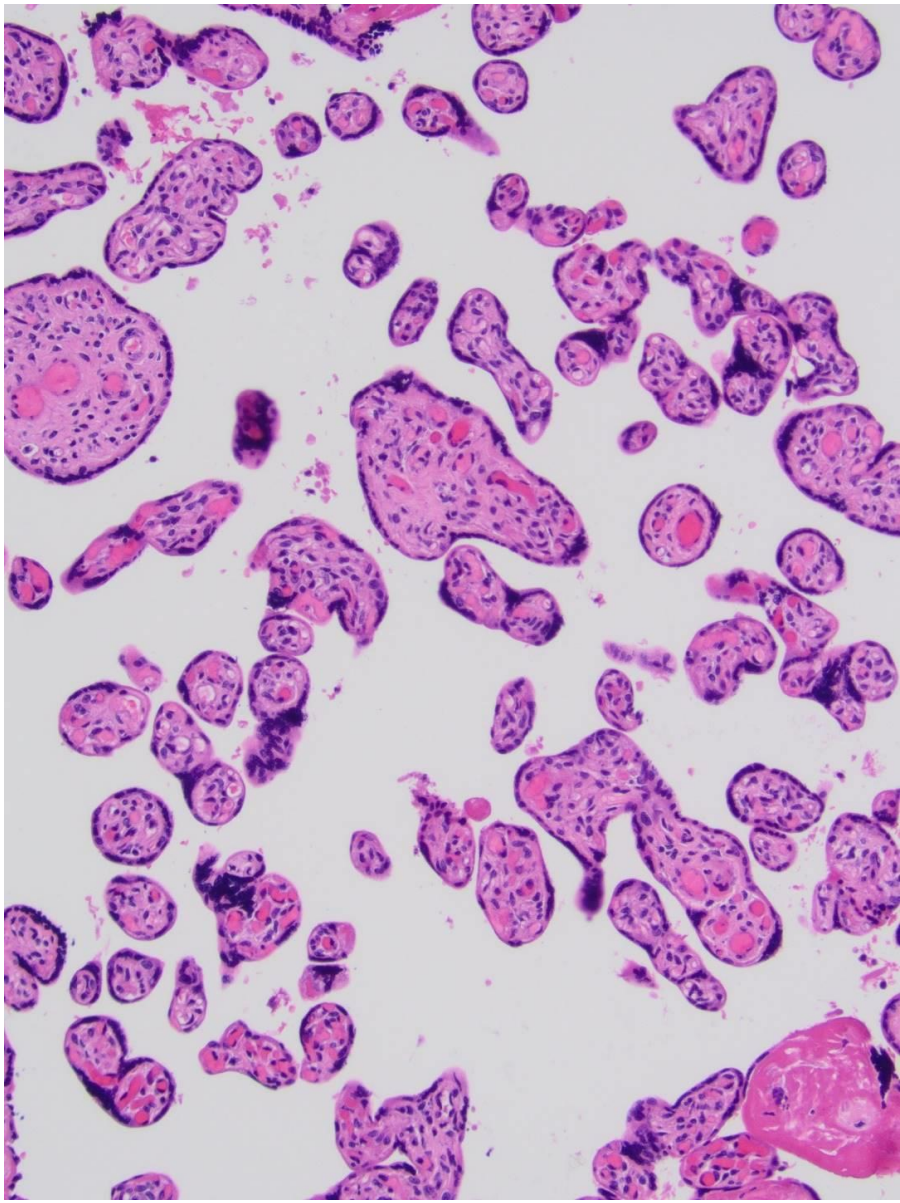


Higher power (20X)

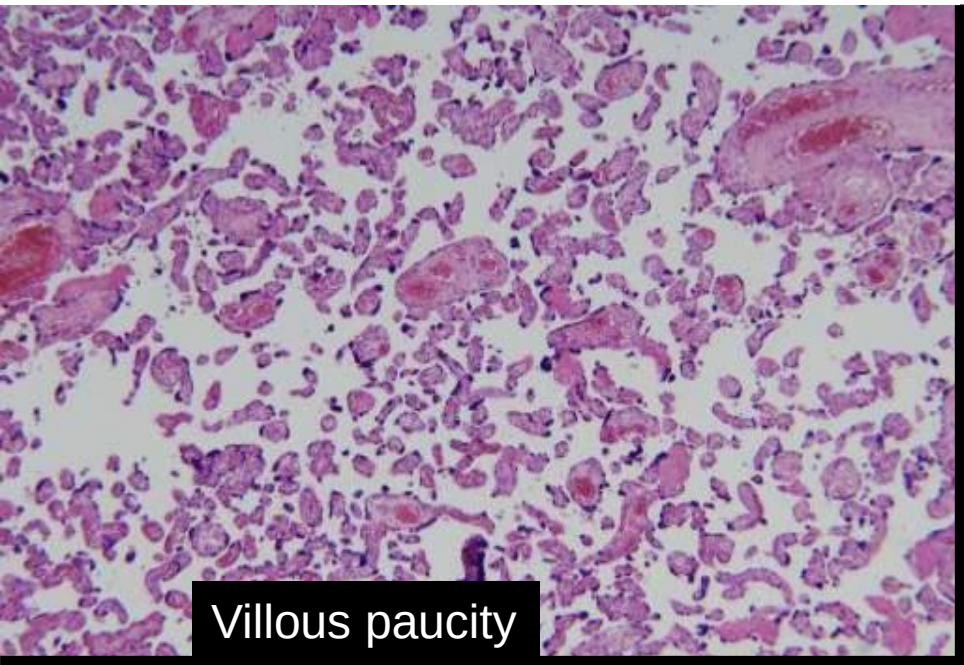
Villous crowding

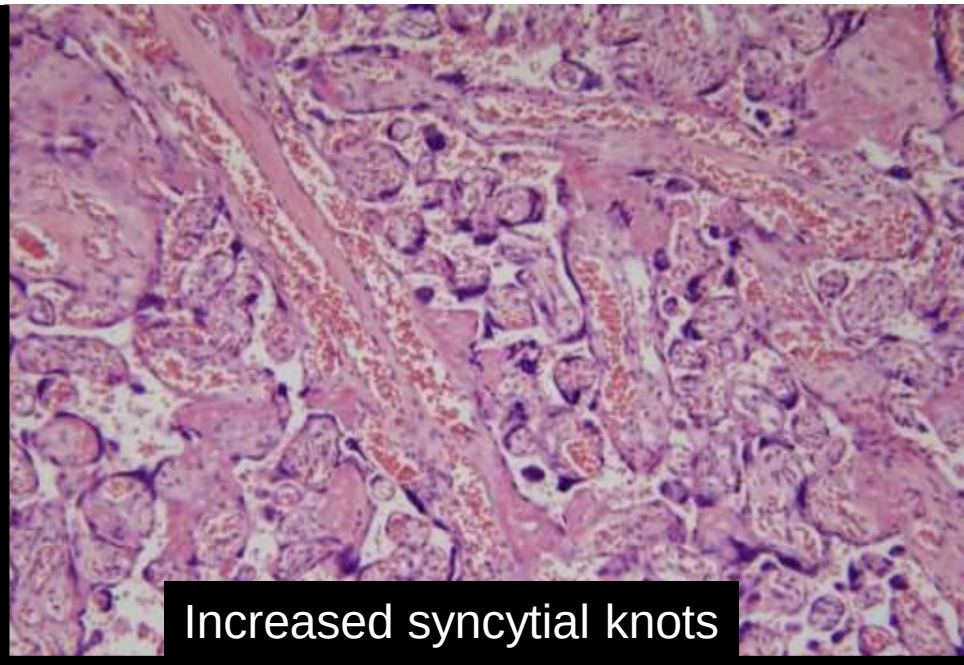


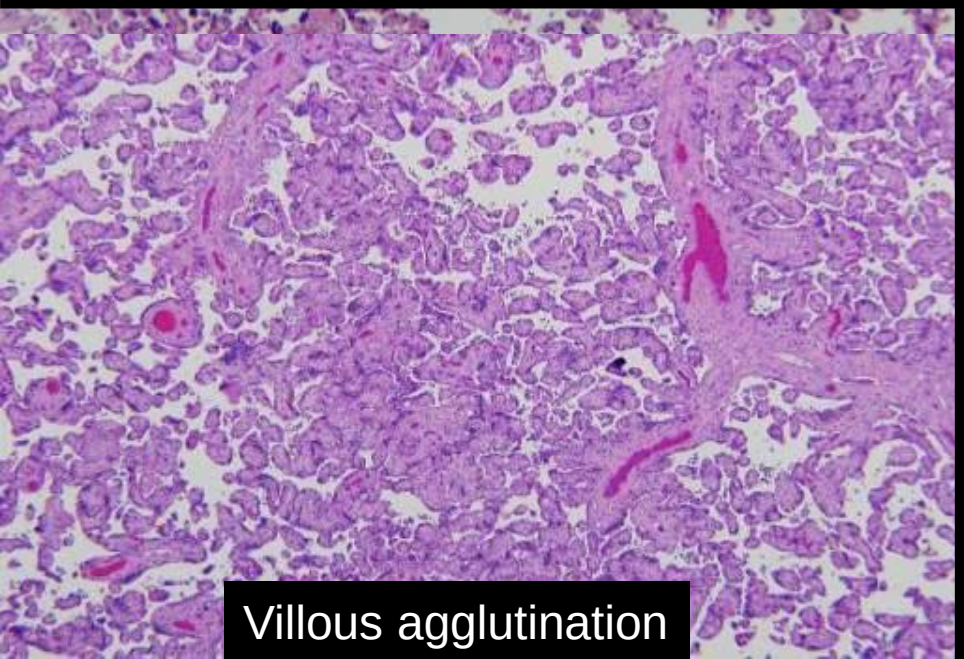
Villous paucity

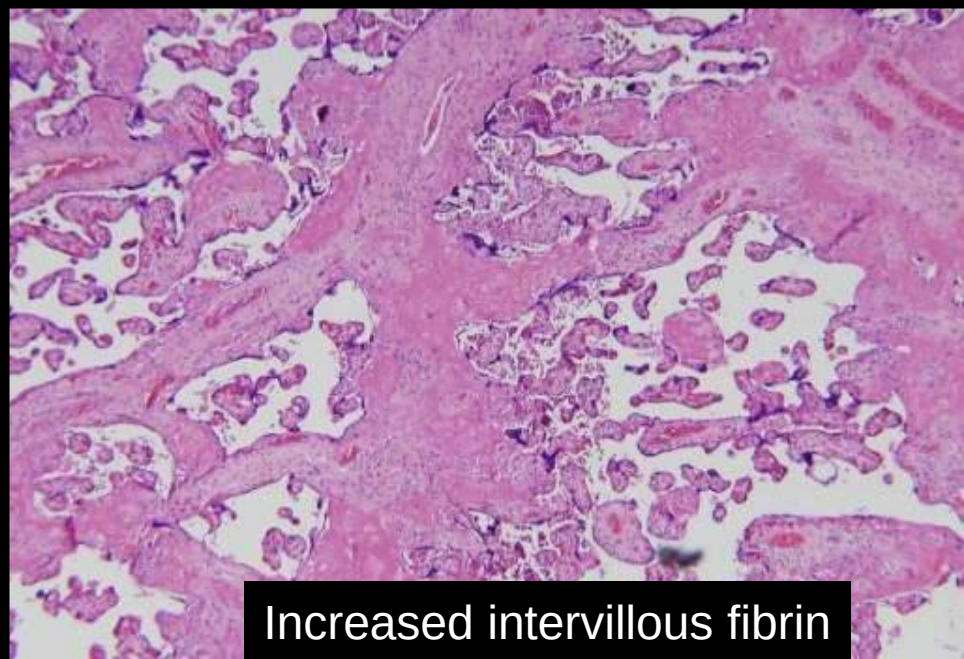


Accelerated maturation: additional images









Distal villous hypoplasia

MVM of longer duration and increased severity.

Definition:

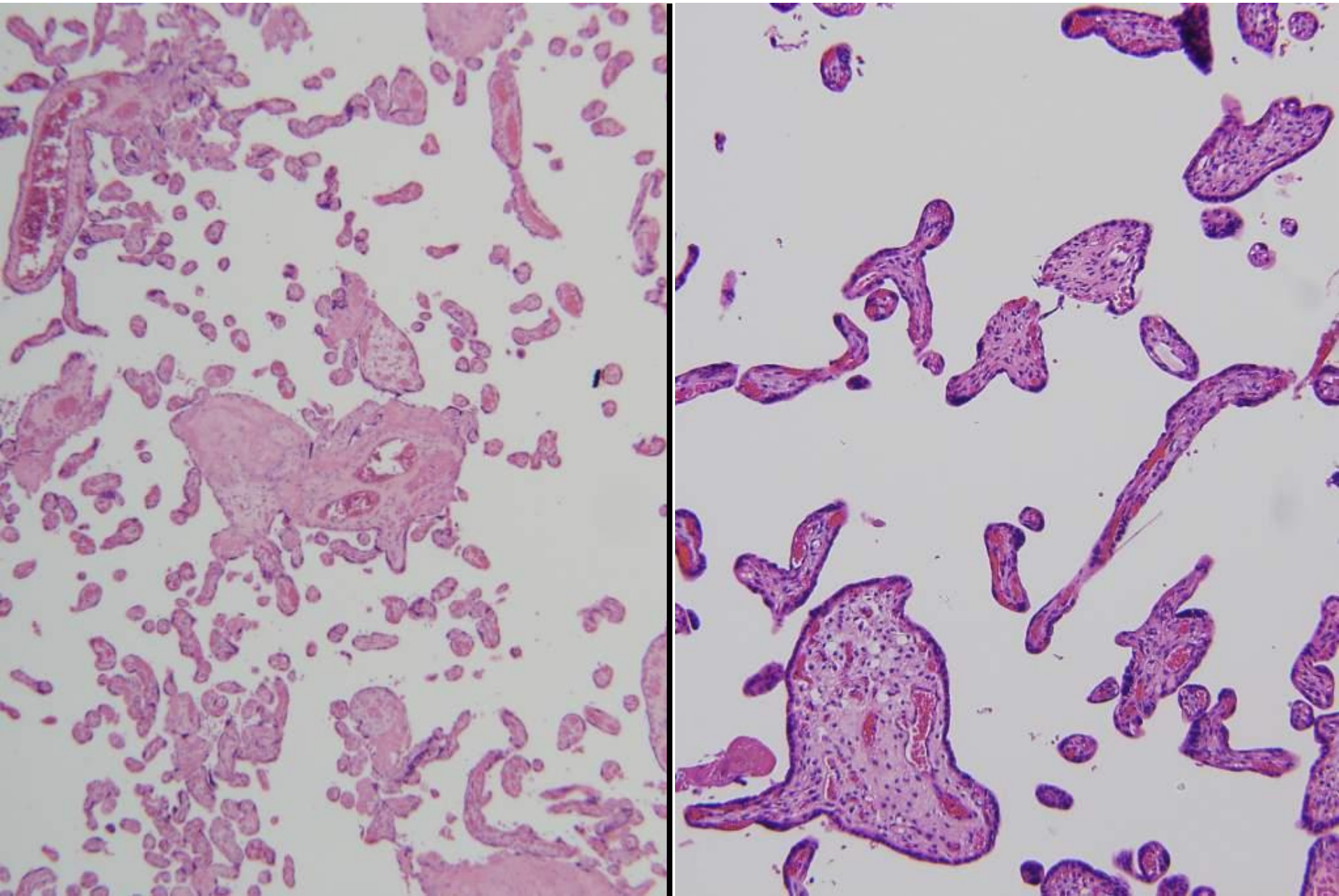
1. Paucity of villi exceeding 30% of total volume
2. Long thin villi with decreased branching
3. Focally increased syncytial knots and villous agglutination

Associations: Fetal and placental weights both < 3rd percentile. Markedly increased fetoplacental weight ratio. Absent or reversed umbilical arterial blood flow by Doppler, IUFD

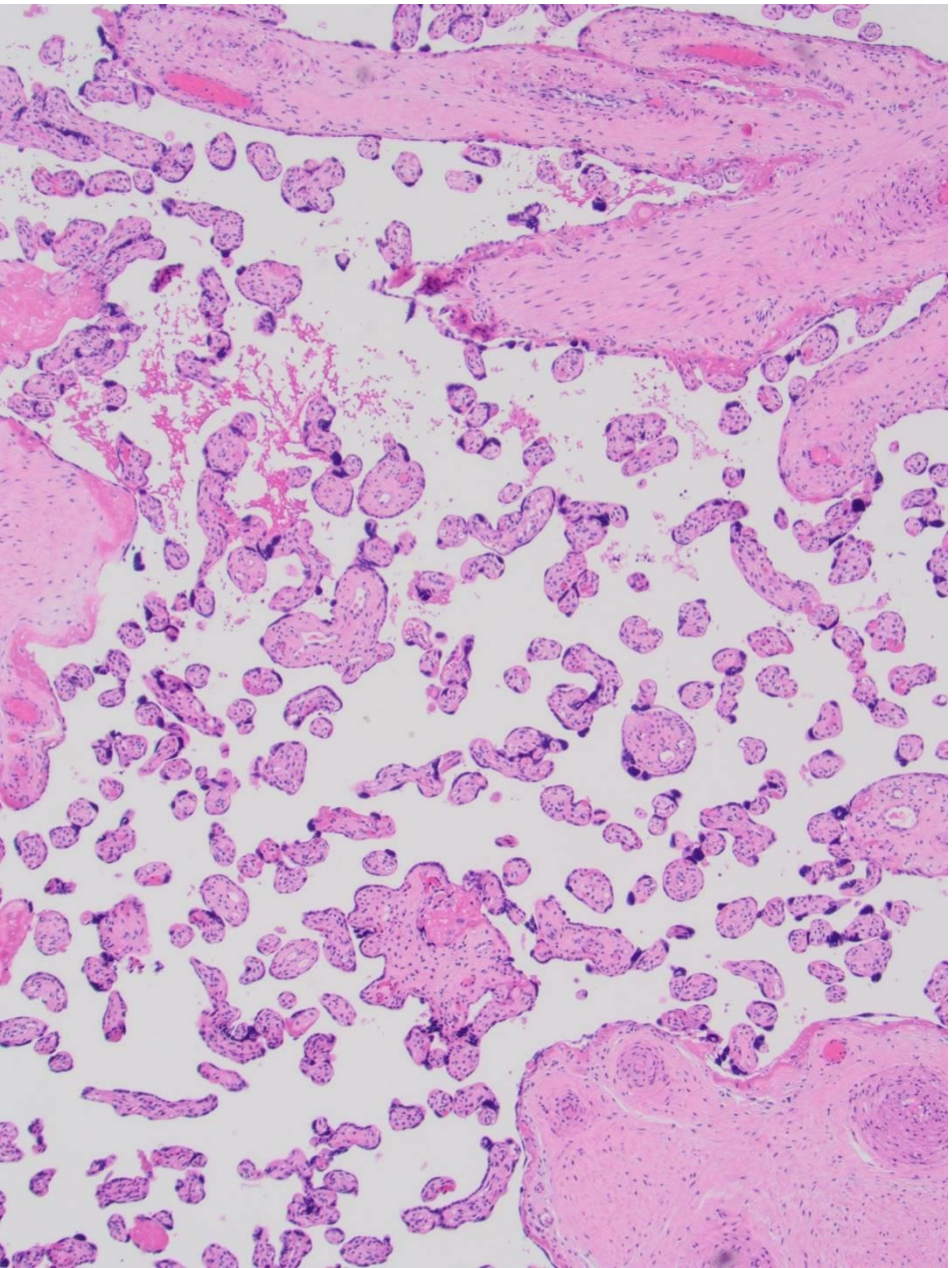
Complications: Pathologically reduced uptake of nutrients, fetal osteopenia, increased placental vascular resistance

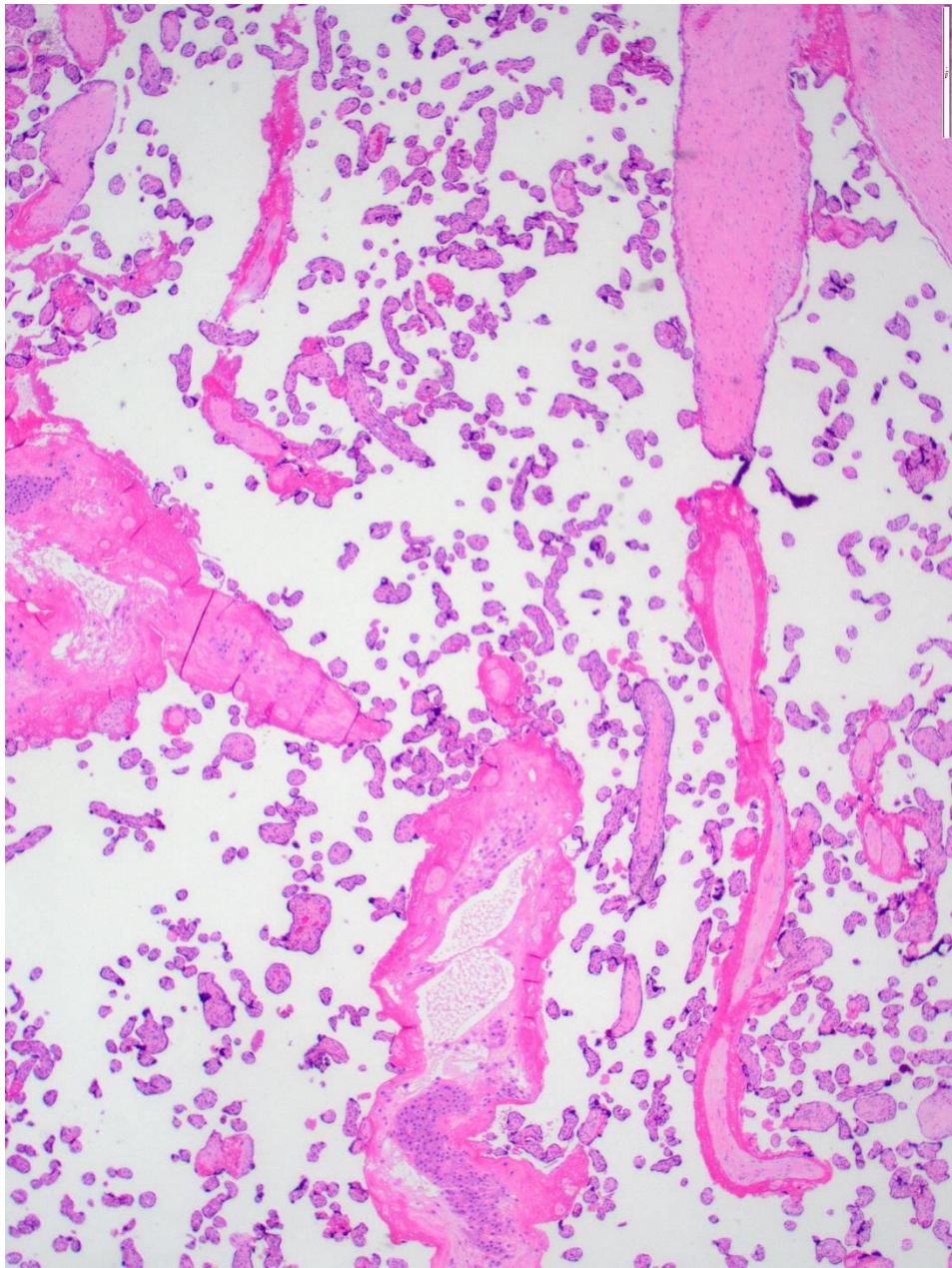
Paucity >30% = Distal villous hypoplasia

correlates with abnormal end-diastolic flow by umbilical doppler



Distal villous hypoplasia: additional images





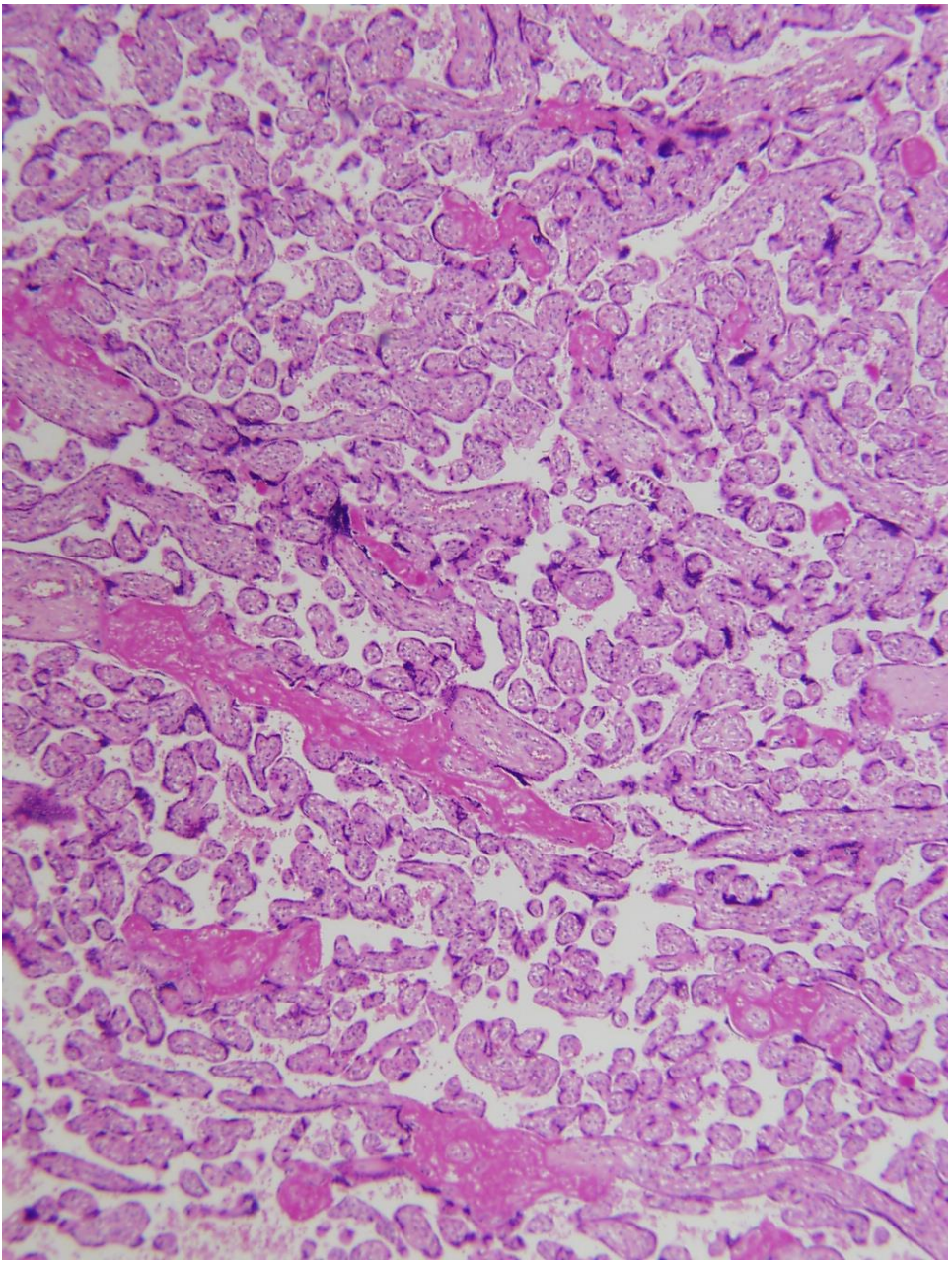
Focally increased syncytial knots
(nonspecific descriptive diagnosis)

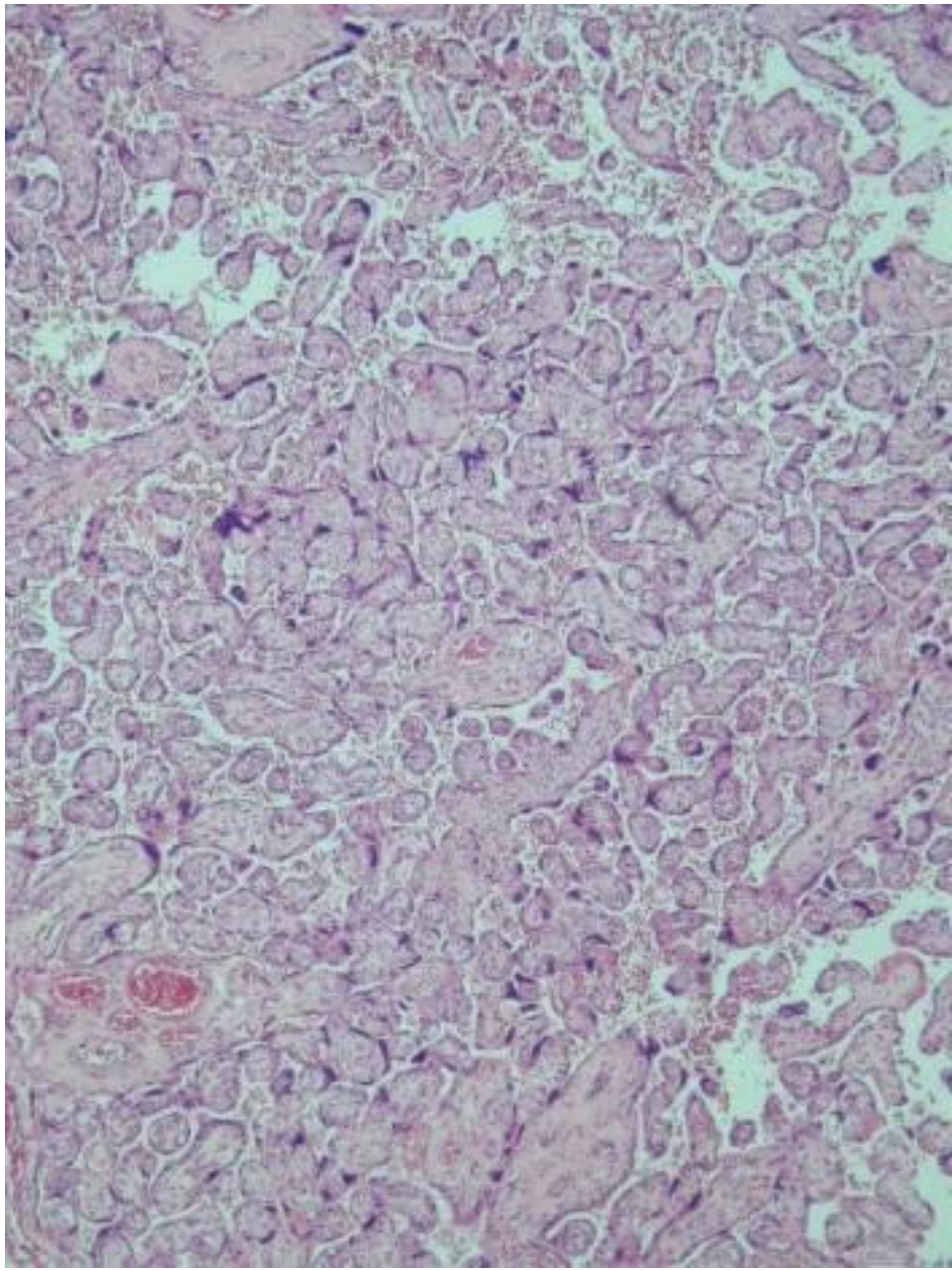
Definition: Clusters of villi with crowding, without paucity, showing some combination of increased syncytial knots, intervillous fibrin, and villous agglutination.

Associations: Preeclampsia at term, Chronic hypertension, Borderline FGR

Complications: Release of ischemia-related mediators into maternal circulation

Focally increased syncytial knots





Categories of Placental Pathology

Fetal stromal-vascular lesions:

1. Maldevelopment
   - Delayed villous maturation
   - Villous dysmaturity
   - Villous capillary lesions
   - Dysmorphic villi
   - Mesenchymal dysplasia
2. Malperfusion
   - Global (partial): umbilical cord obstruction
   - Segmental (complete): fetal thrombosis
3. Loss of integrity
   - Edema (hydrops)

Fetal stromal-vascular maldevelopment
Delayed villous maturation

Definition:

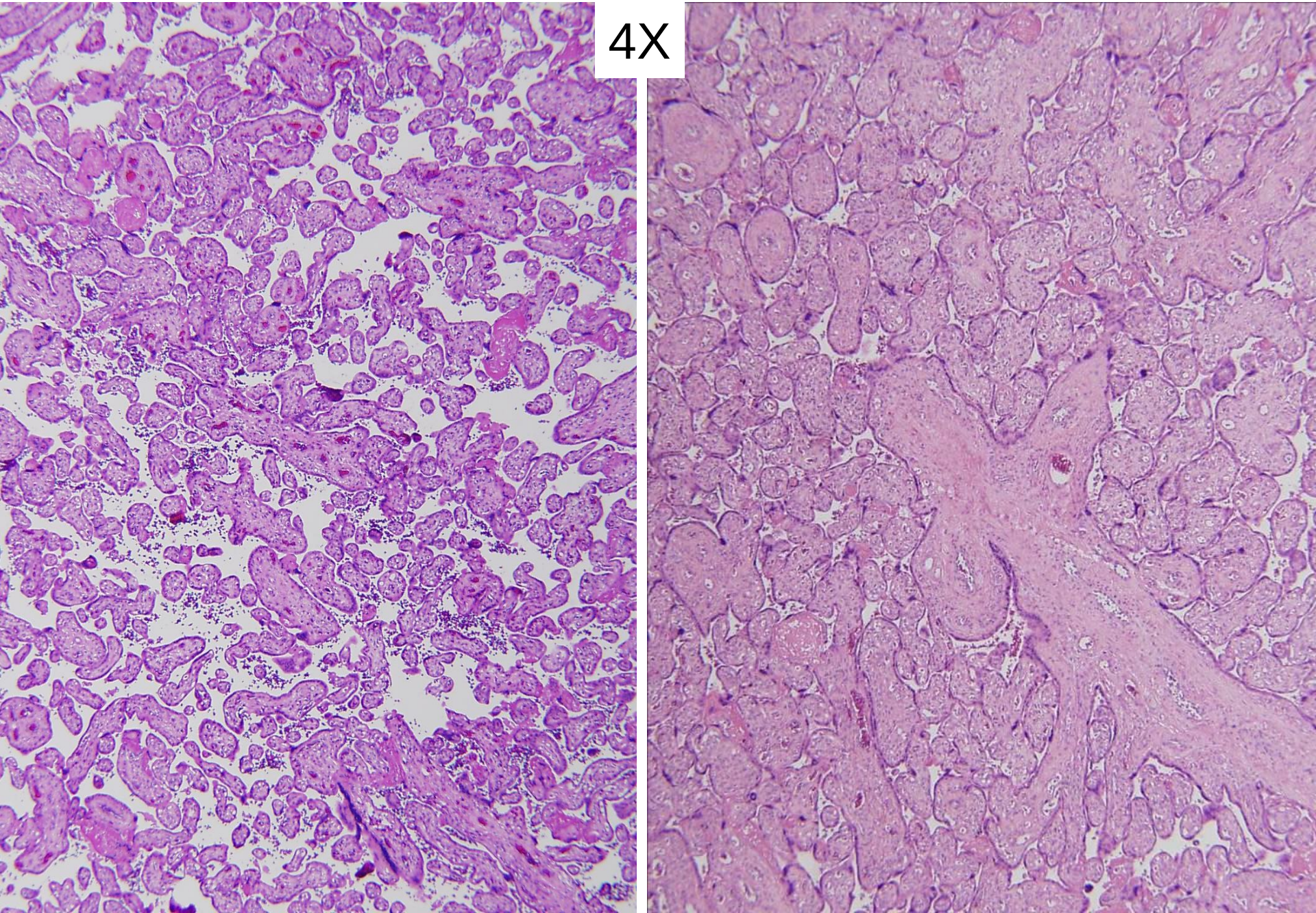
1. Enlarged villi/ decreased intervillous space (> 30% of villi)
2. Cellular villous stroma: fibroblasts, Hofbauer cells, pericytes
3. Central capillaries with ↓vasculo-syncytial membranes
4. Thick trophoblast layer with ↑ number of nuclei

Associations: large placenta, ↓ fetoplacental weight ratio, diabetes (increased fetal insulin), obesity, excessive pregnancy weight gain,

Complications: increased placental demand, decreased placental function, stillbirth, subgroup of FGR

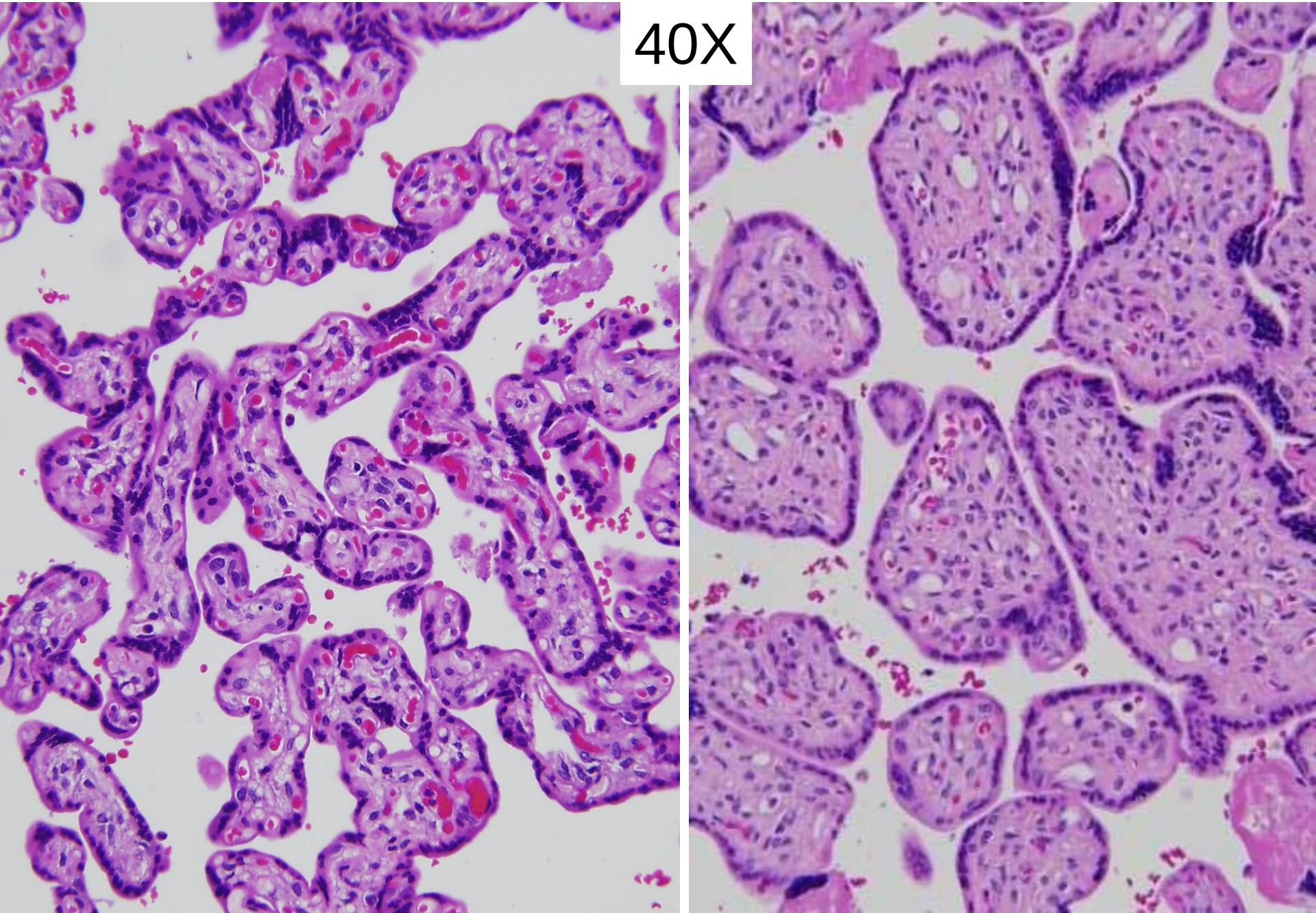
Normal term villi

Delayed villous maturation

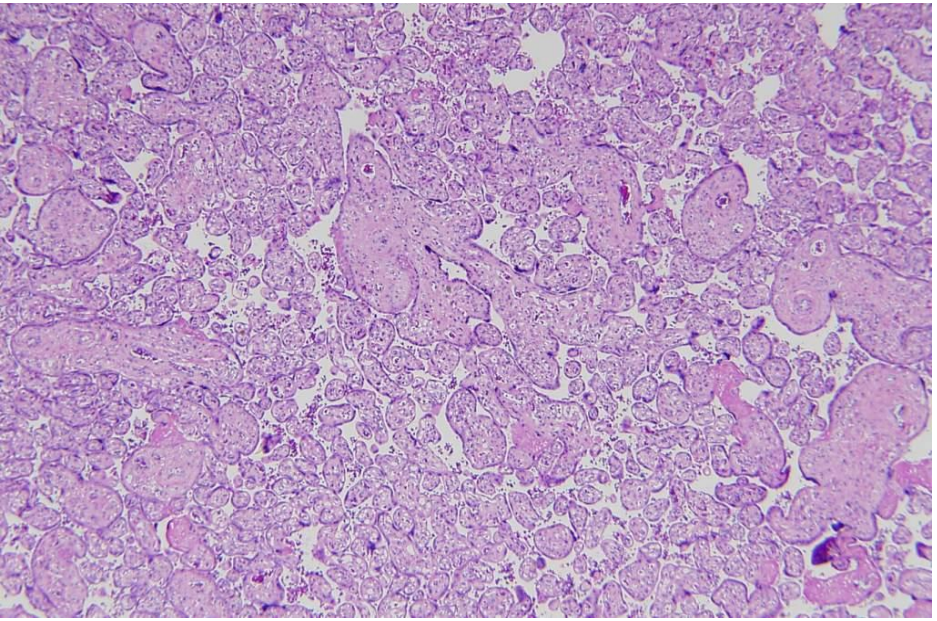


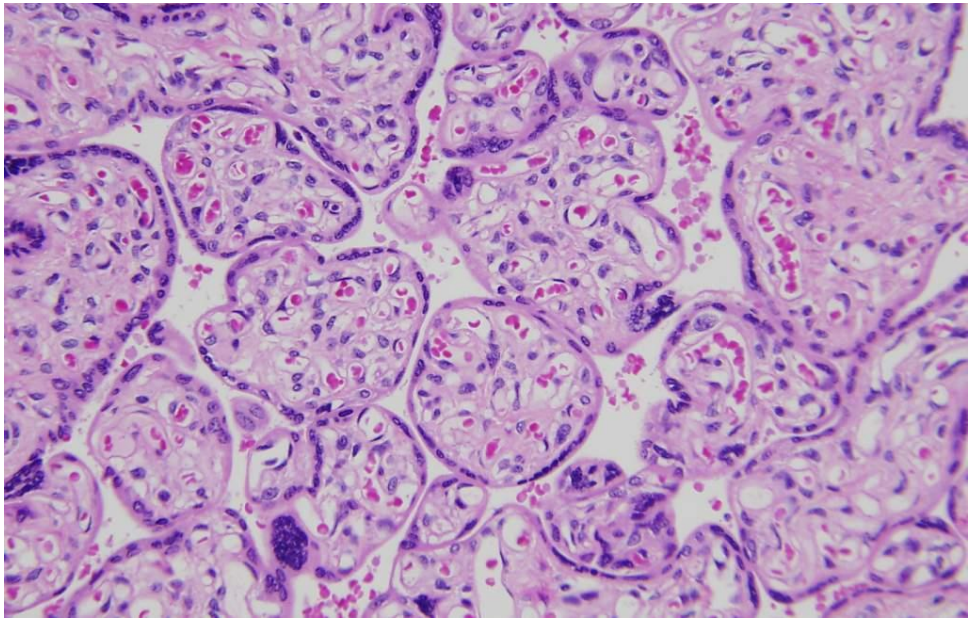
Normal term villi

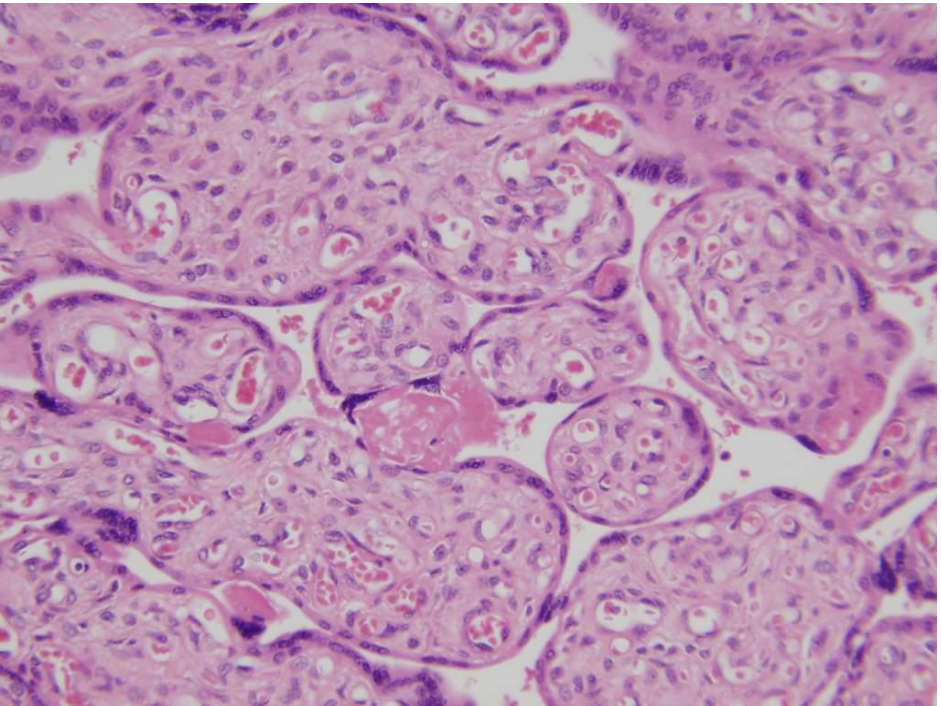
Delayed villous maturation

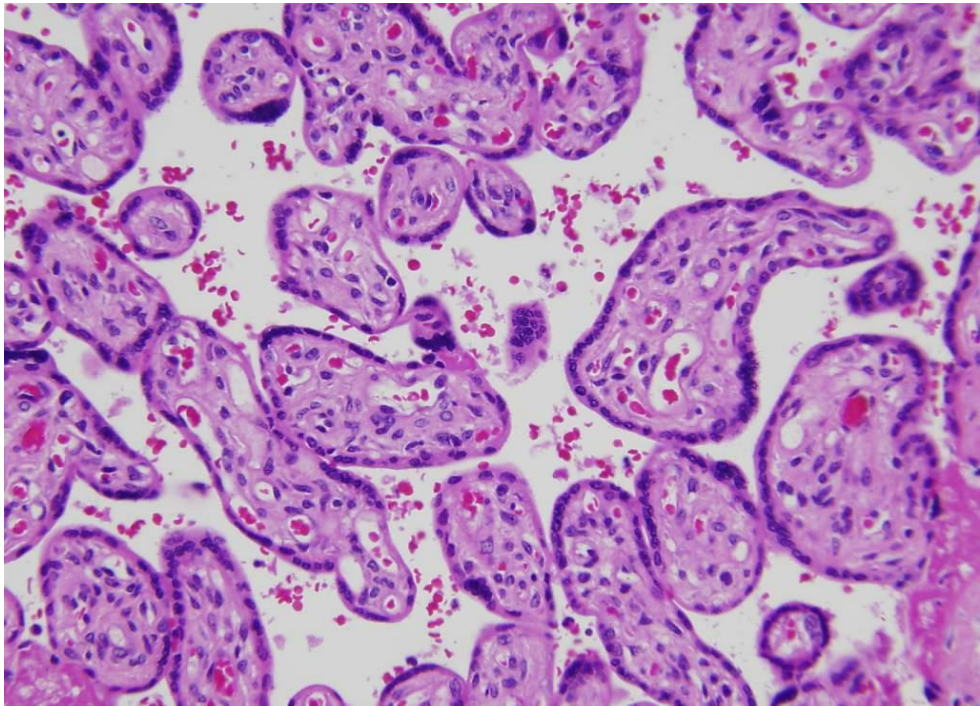


Delayed villous maturation: additional images









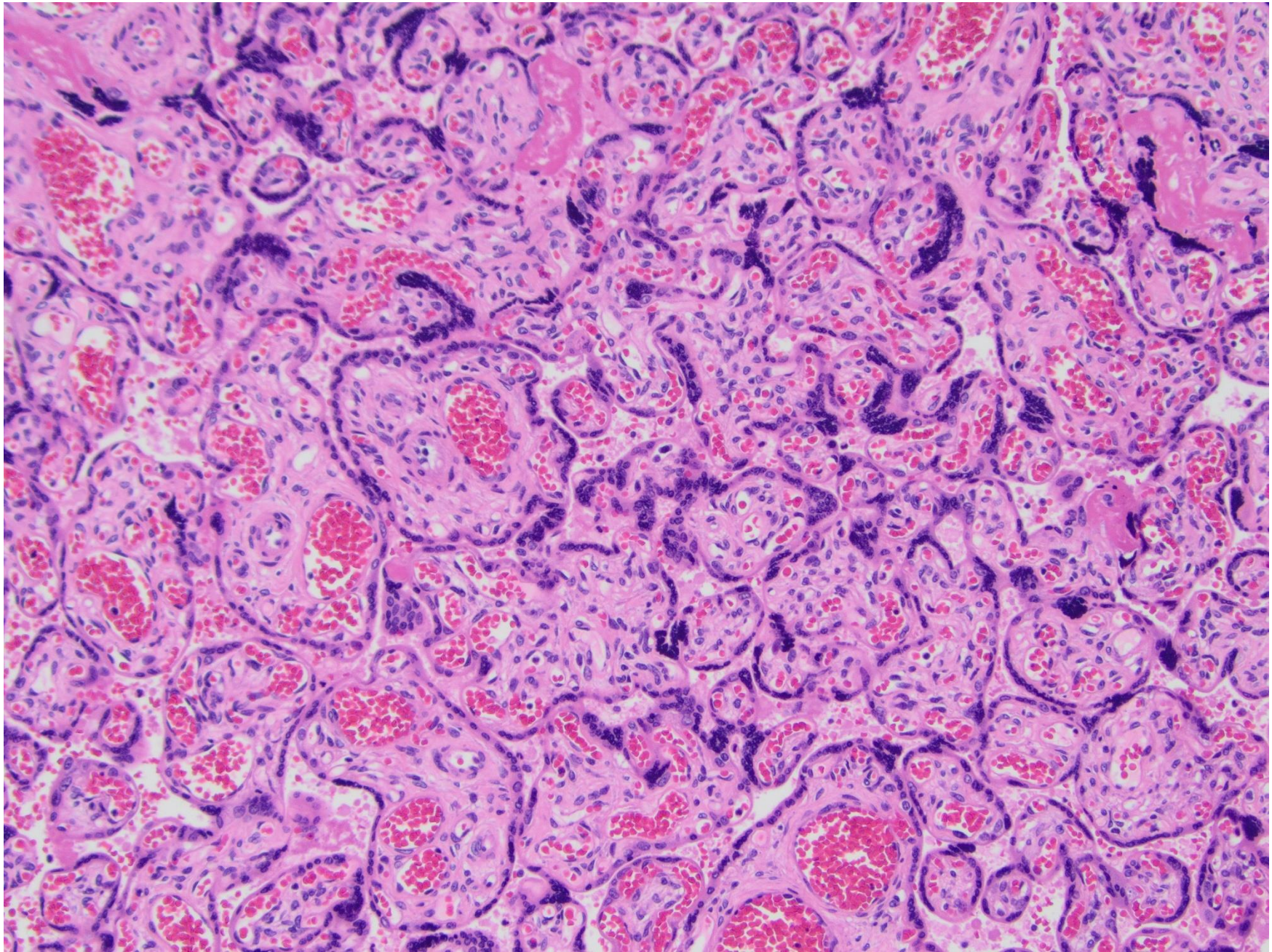
Villous dysmaturity

Definition: Delayed villous maturation with focally increased syncytial knots (alternating delayed/accelerated maturation)

Associations: placenta and infant in “normal” weight range, maternal diabetes or obesity with pregnancy hypertension or FGR

Complications: abnormal villous function, release of ischemia-related mediators into maternal circulation

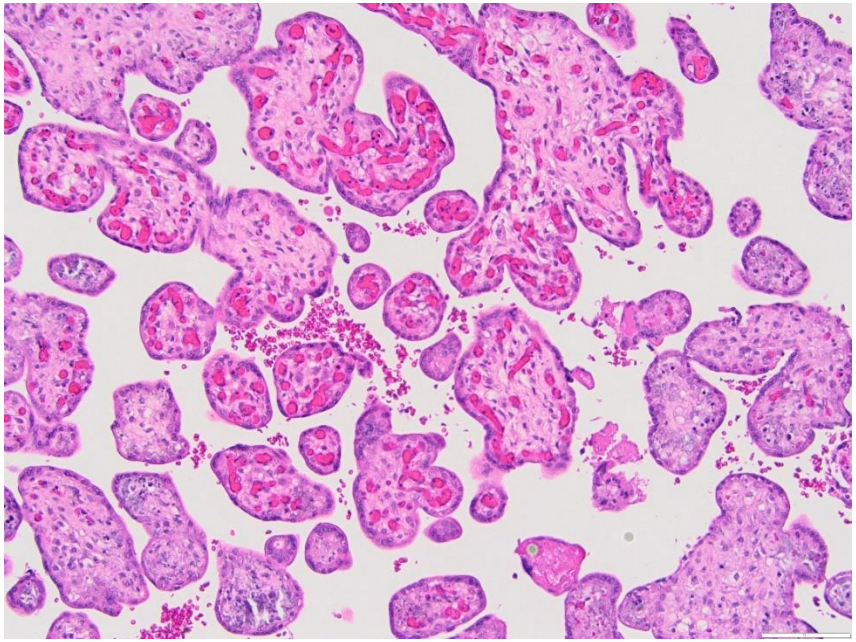
Villous dysmaturity

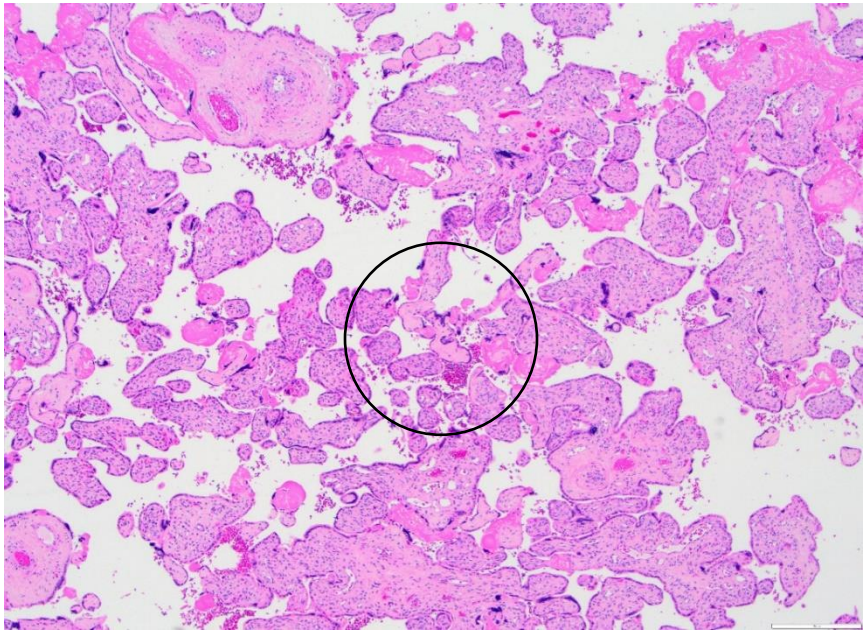


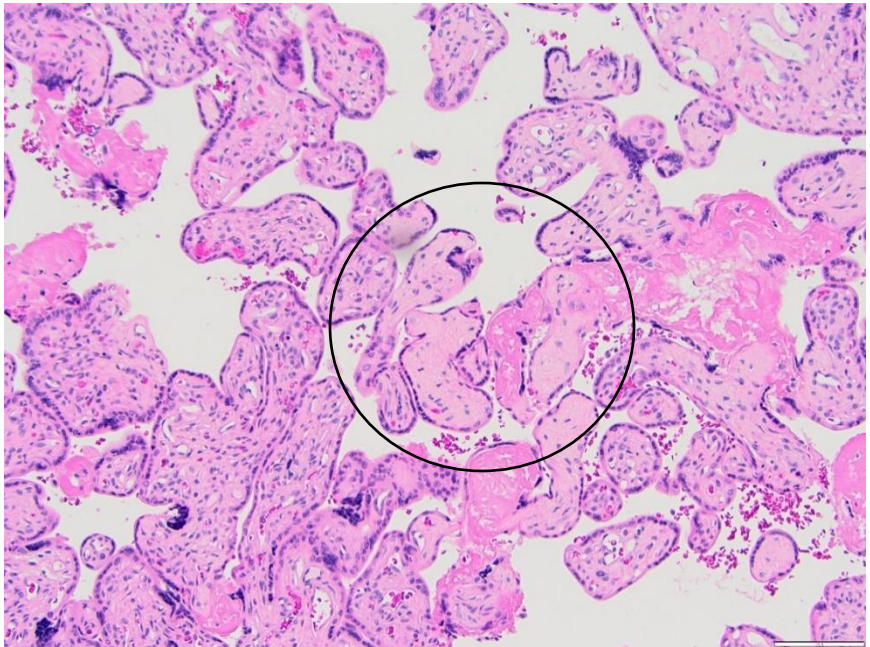
Differential diagnosis

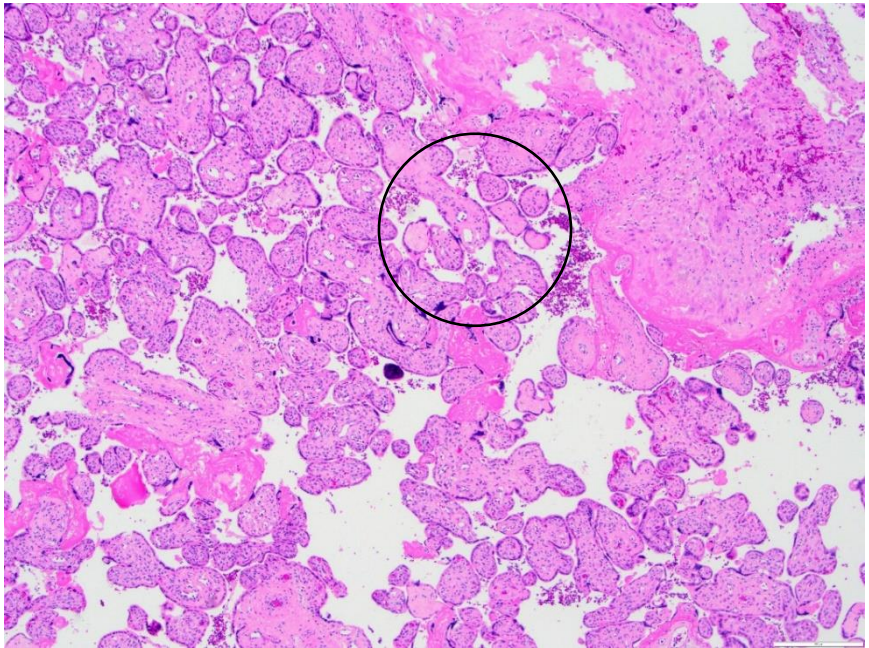
1. “Delayed villous maturation like -pattern” seen with fetal vascular malperfusion due to chronic umbilical cord obstruction
2. Diffuse villous edema (hydropic placenta)
3. Patchy nonspecific villous edema
4. Foci of neovillogenesis

“*Delayed villous maturation-like pattern”*
global FVM/ chronic partial/ intermittent UC obstruction

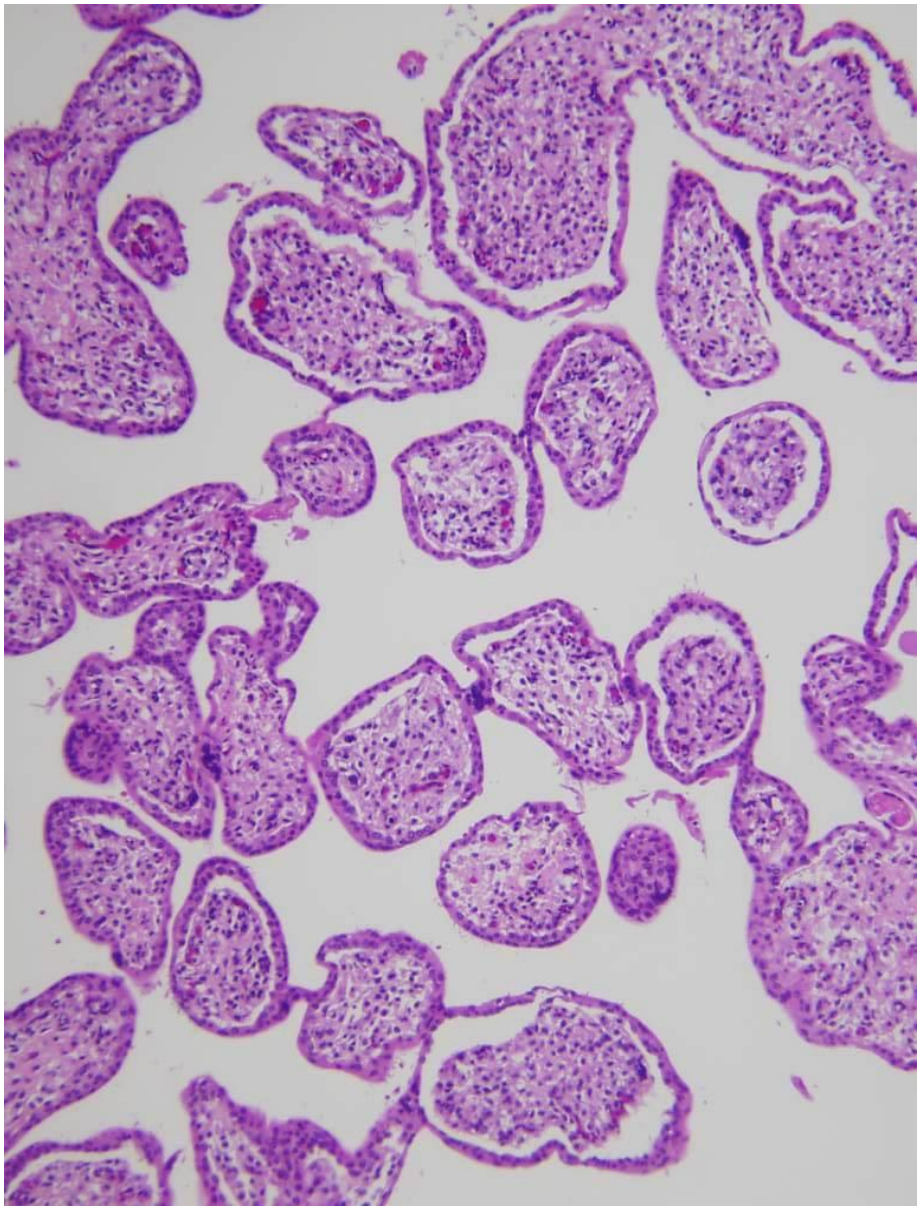




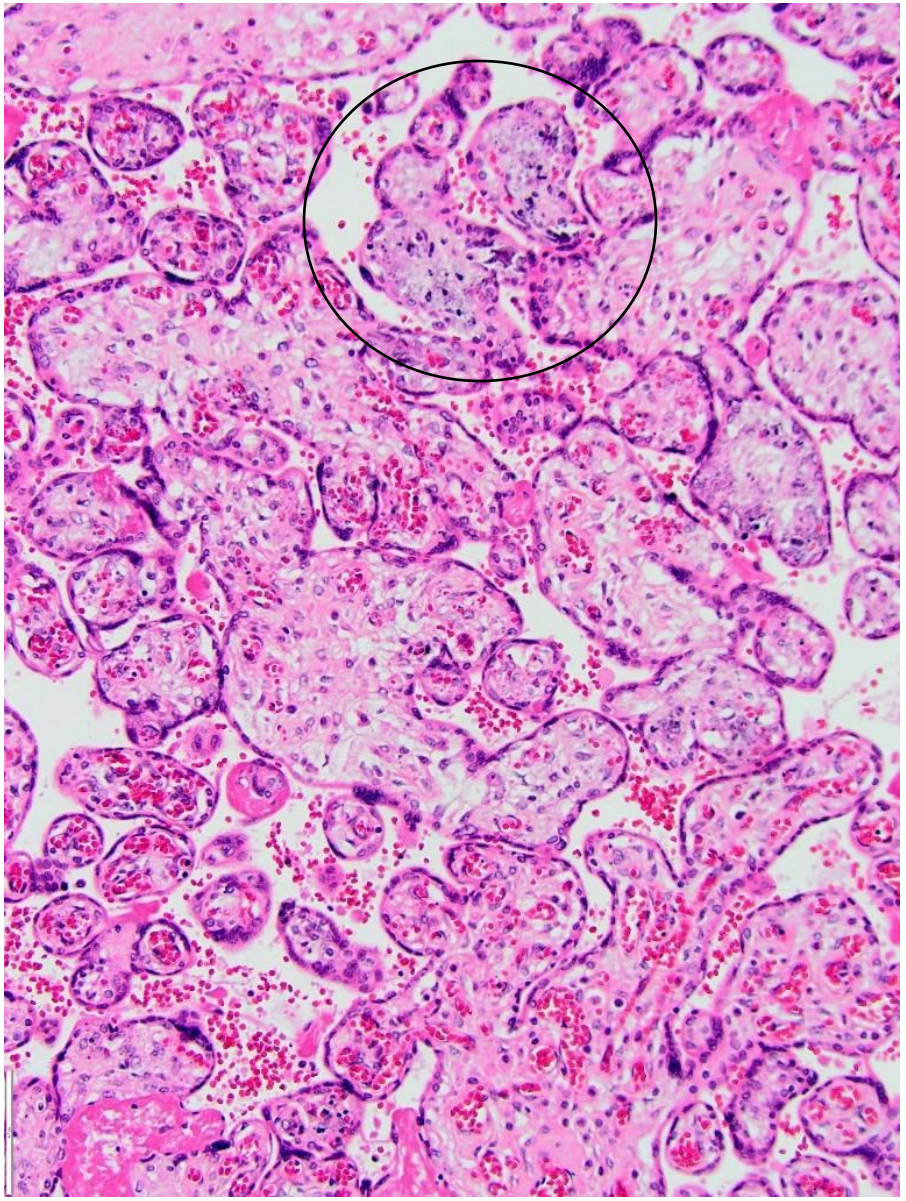




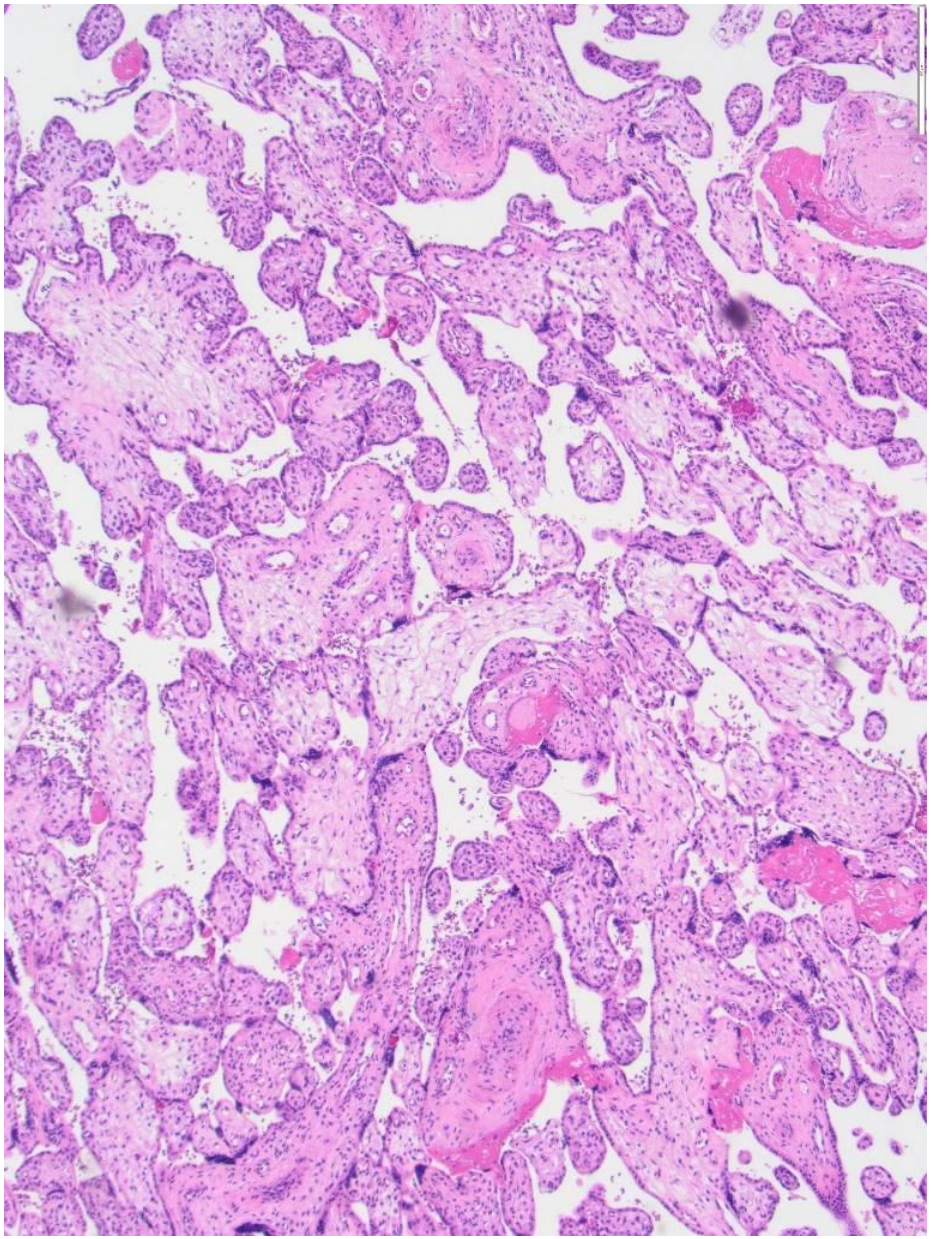
Villous edema due to Hydrops fetalis

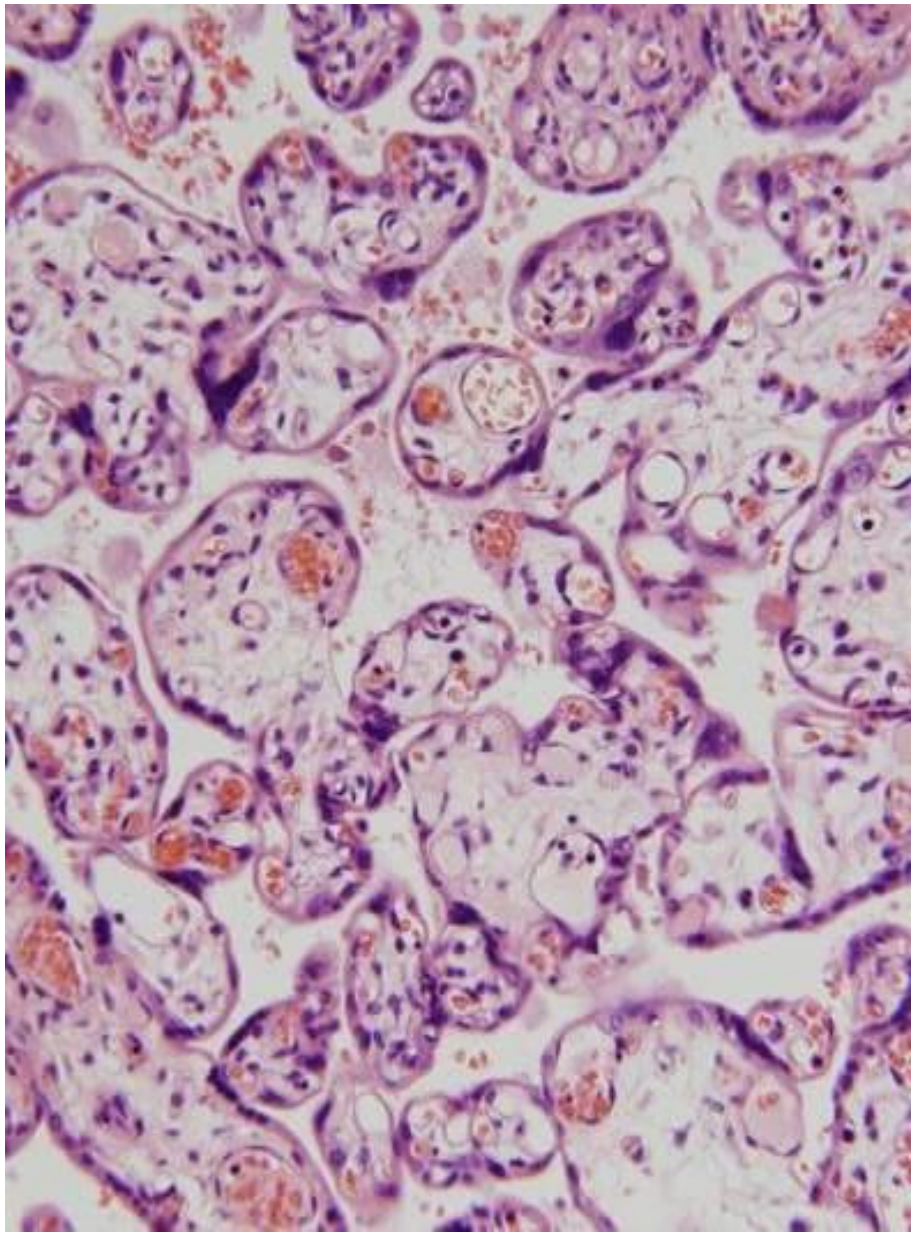


Villous edema with stromal vascular karyorrhexis

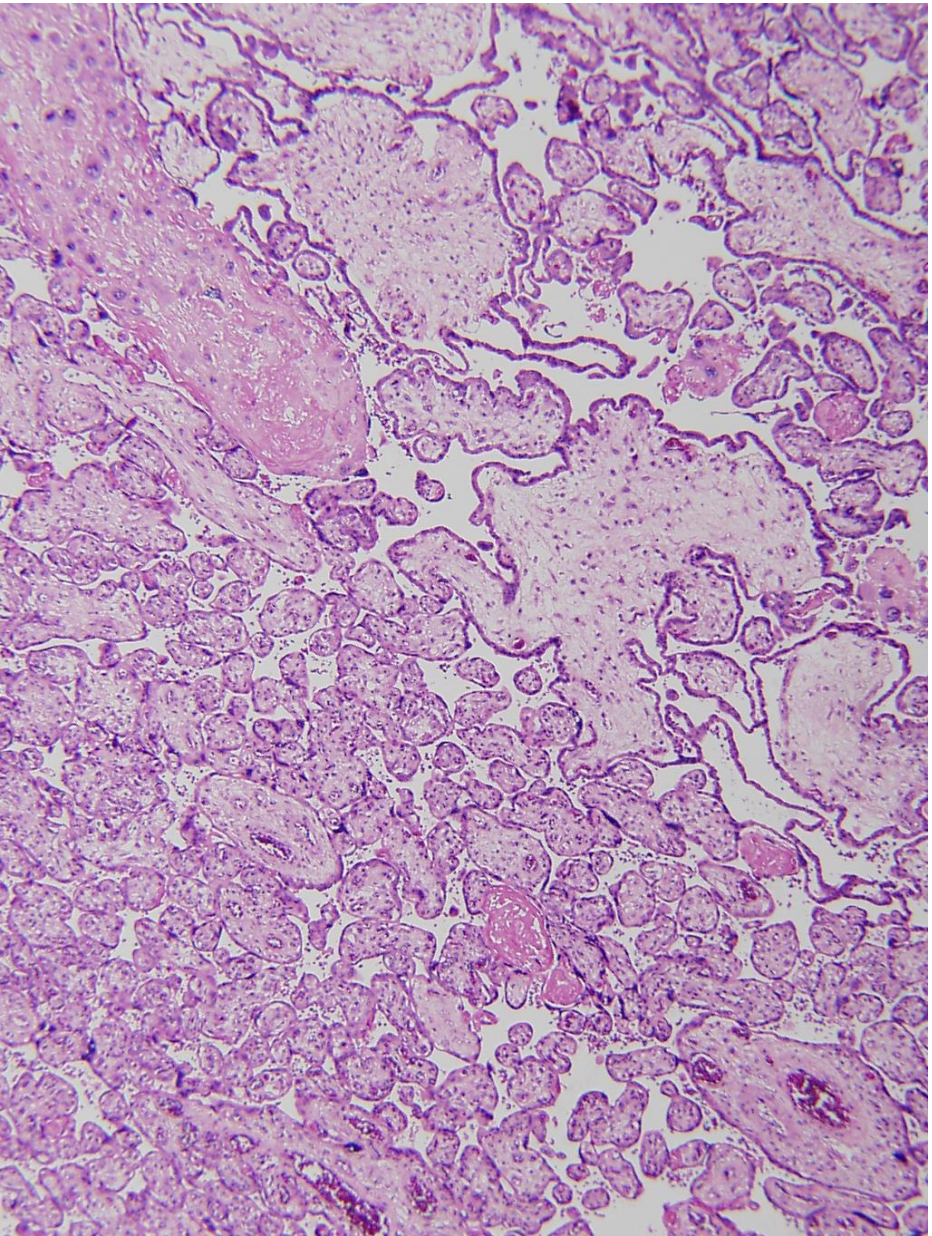


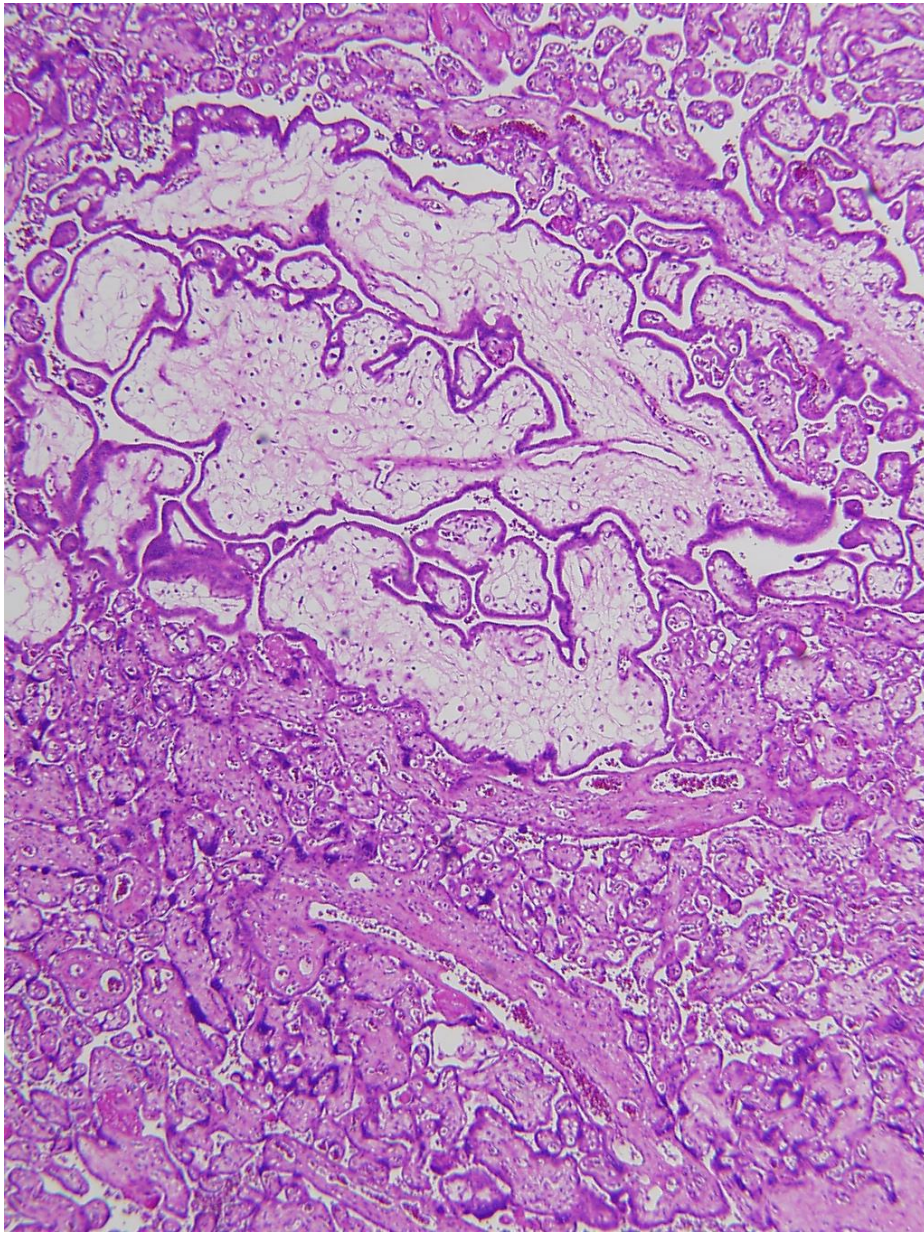
Patchy nonspecific villous edema (NOS)





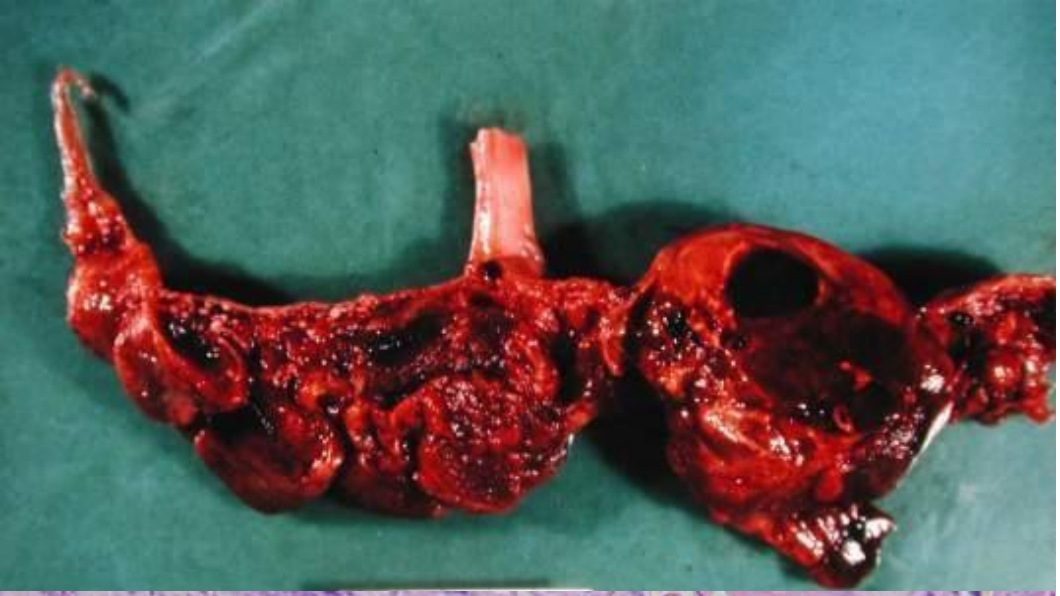
Foci of “Neovillogenesis”

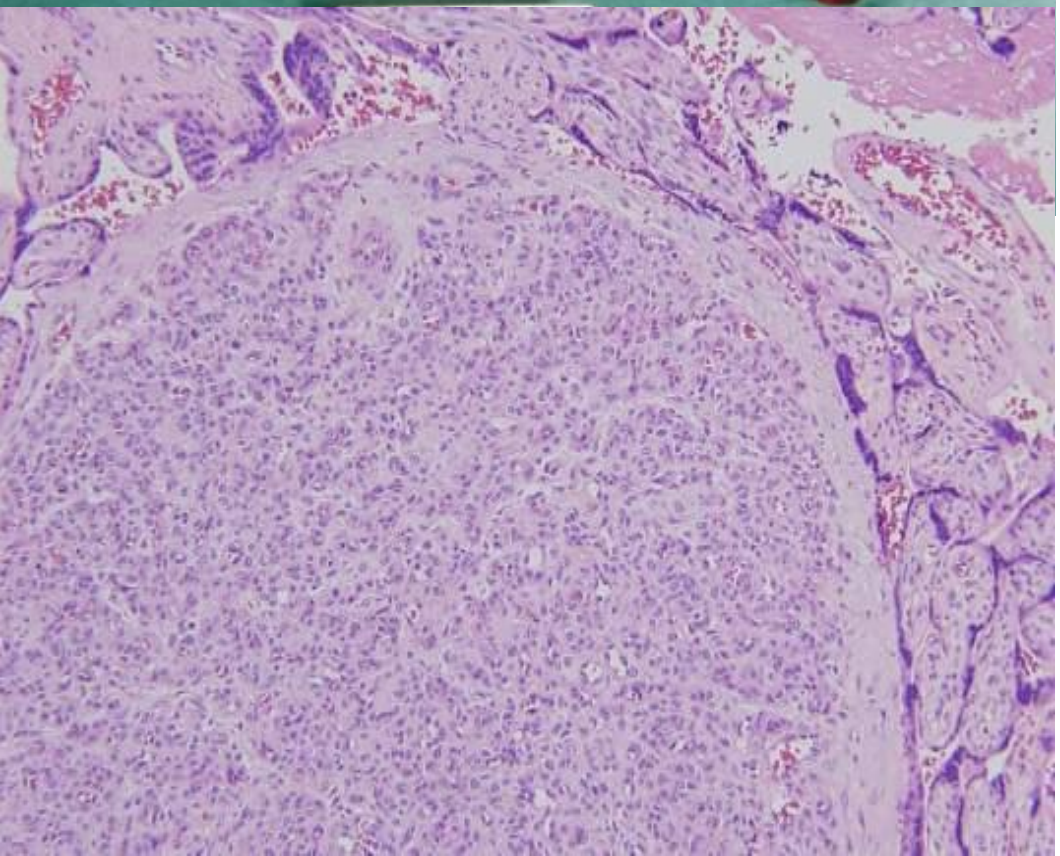




Fetal villous capillary lesions

- Chorangioma (single/ multiple)
  (1-2% of all placentas)
- Villous chorangiosis
  (5-10% of term placentas)
- Multifocal chorangiomatosis
  (<1% of all placentas)





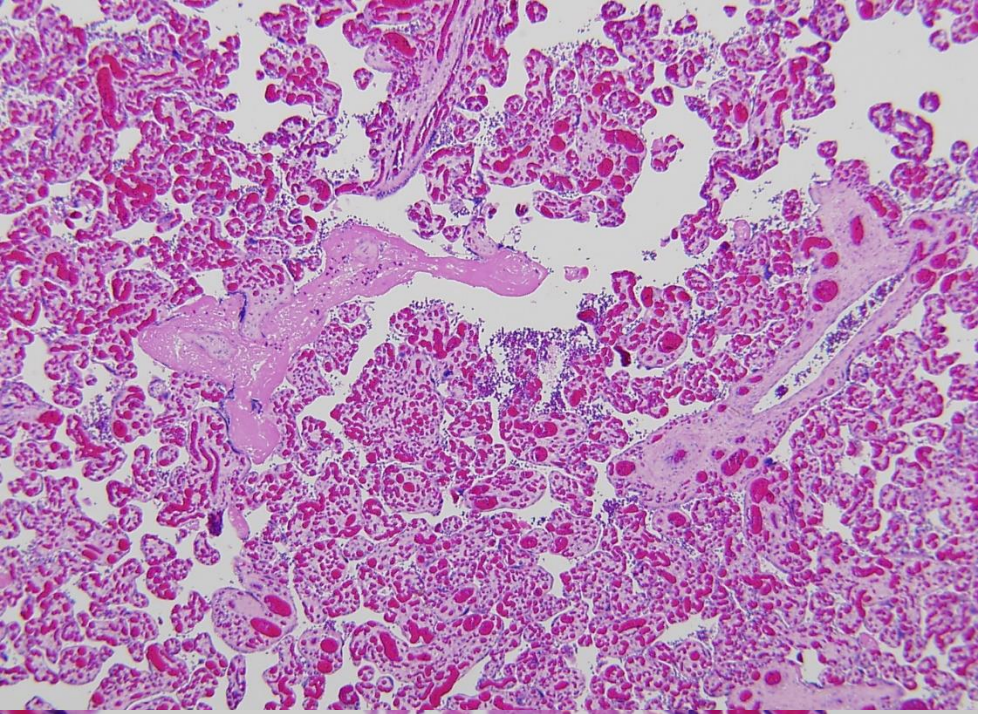
Chorangioma

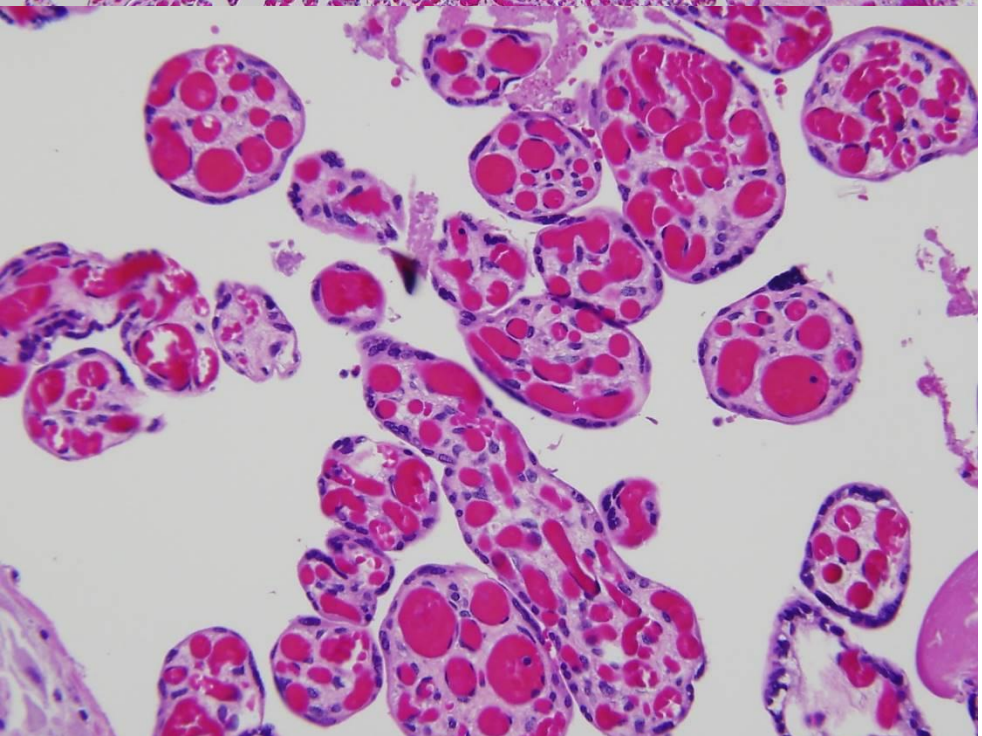
(placental hemangioma)

- GA: 32-36 weeks

- Increased in:
  - – Twins
  - – Preeclampsia

- Complications (rare):
  - Sequestration of platelets
  - A-V shunt with hydrops
  - Fetal growth restriction



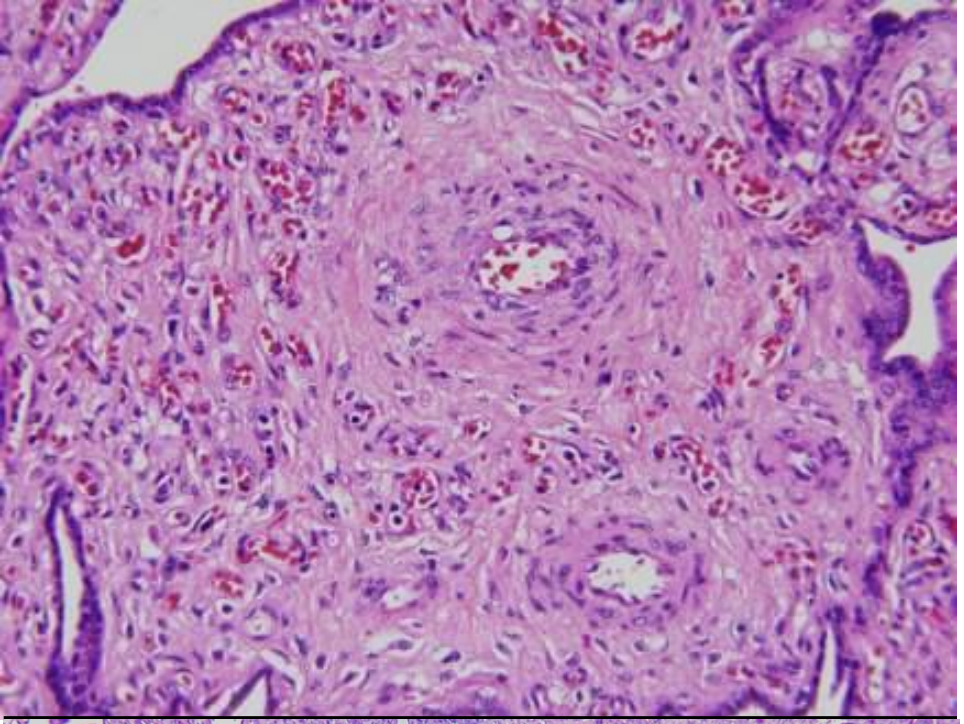


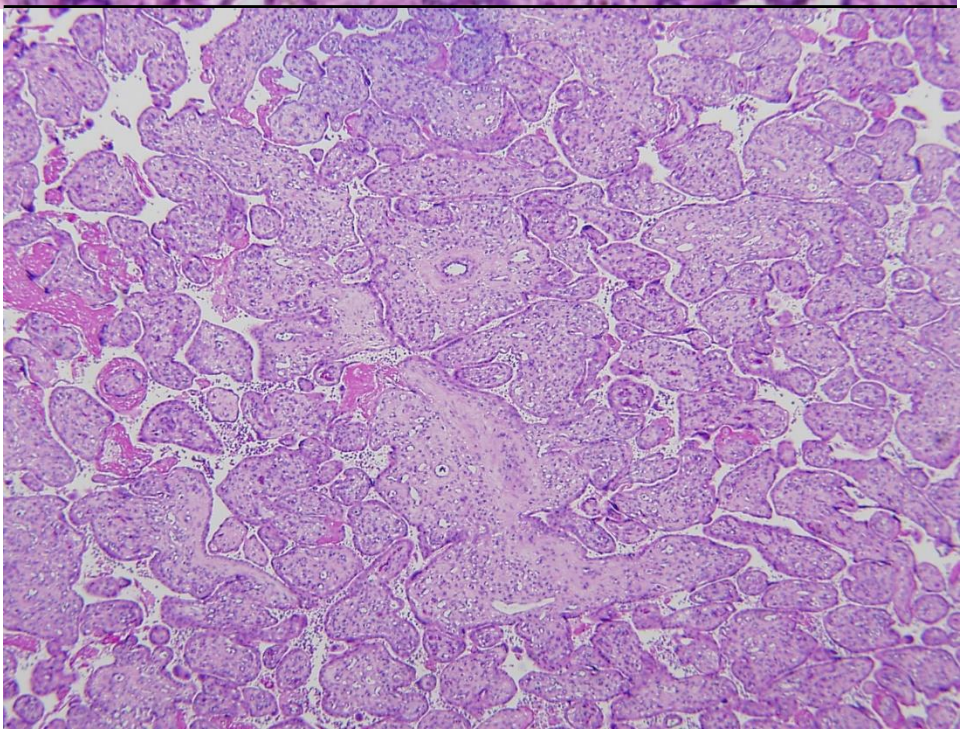
Villous chorangiosis

Definition: 10 capillaries per villus in > 10 villi several different areas + some foci with 15-20 capillaries

Pathophysiology: Angiogenesis due to maternal hypoxemia or hyperglycemia

Clinical: High altitude, smoking, excessive air pollution, maternal anemia, diabetes





Multifocal chorangiomatosis

Pathology: Multiple foci of excessive capillary growth at the periphery of immature intermediate and stem villi

Pathogenesis: Adaptive response to chronic maternal hypoxemia and/or reduced fetal blood flow

Dysmorphic villi ("funny looking villi")

Definition: Abnormal villous pattern, shape, branching, and/or vascularization. Stromal trophoblast inclusions.

Associations: Aneuploid fetus, confined placental mosaicism, idiopathic intrauterine growth restriction, fetal overgrowth disorders

Complications: IUFD, FGR, preterm birth, fetal anomalies; usually not recurrent unless parental chromosomal translocation carrier

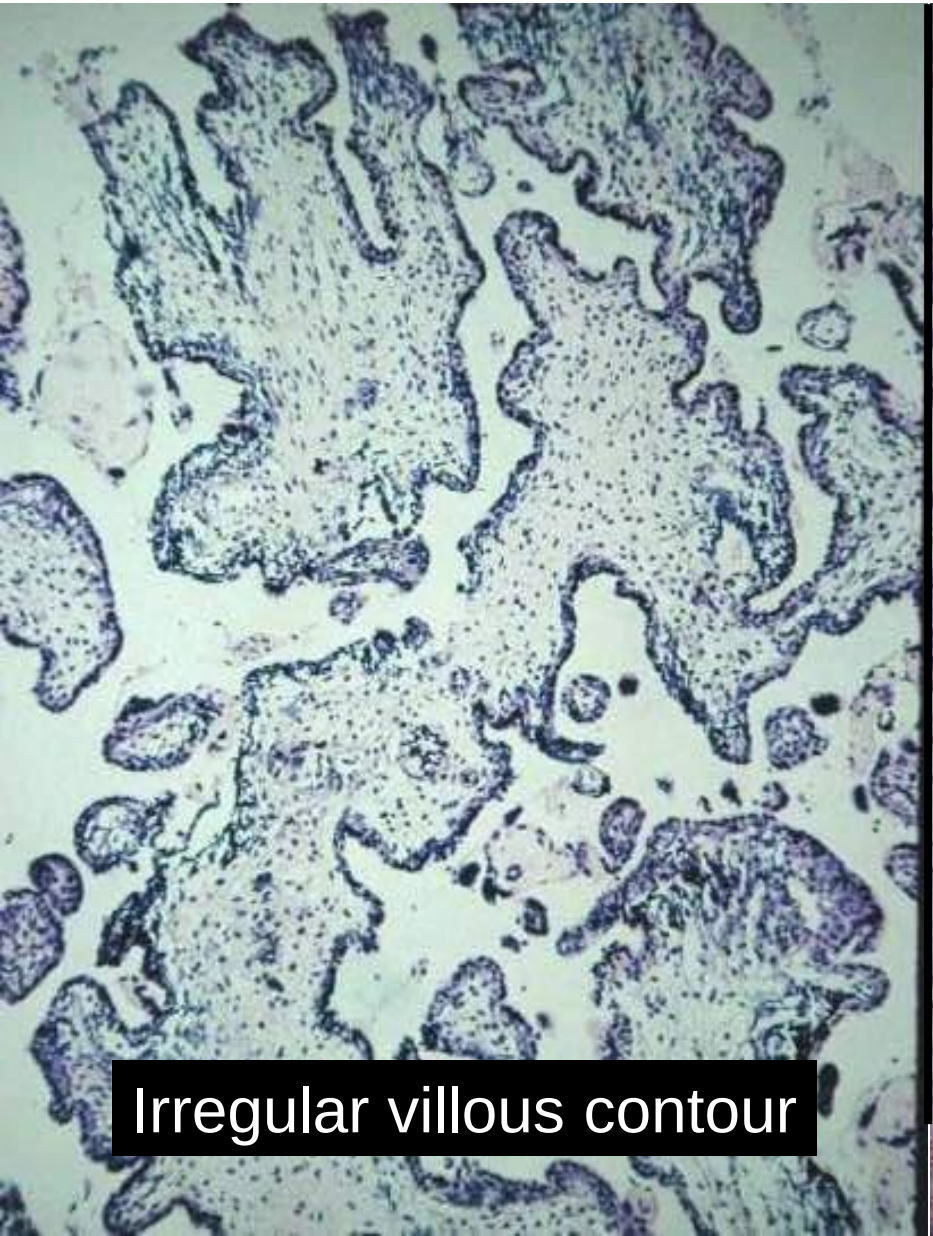
First trimester miscarriages Histologic Features by Karyotype

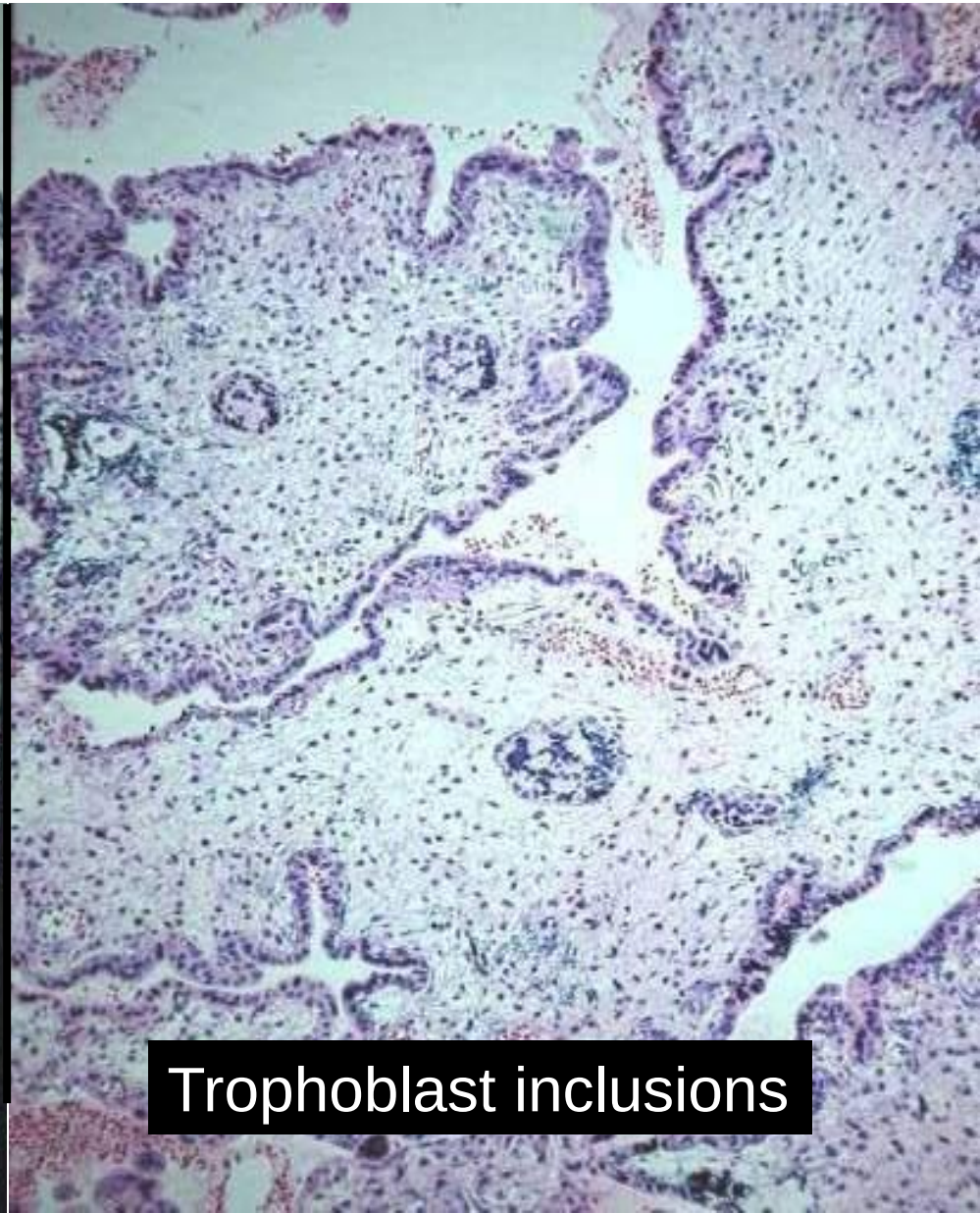
Histologic findings	Normal karyotype	Abnormal karyotype
	(N=318)	(N=350)
Dysmorphic features	2.2%	17.4%*
Chronic histiocytic intervillositis	4.4%*	0.3%
Massive perivillous fibrin(oid)	5.4%*	0.9%
Decidual plasma cells	5.4%*	3.7%
Diffuse chronic deciduitis	9.1%*	4.0%
Chronic villitis	1.3%	0.3%
Decidual vasculopathy	0.6%	0

* $p<0.050$

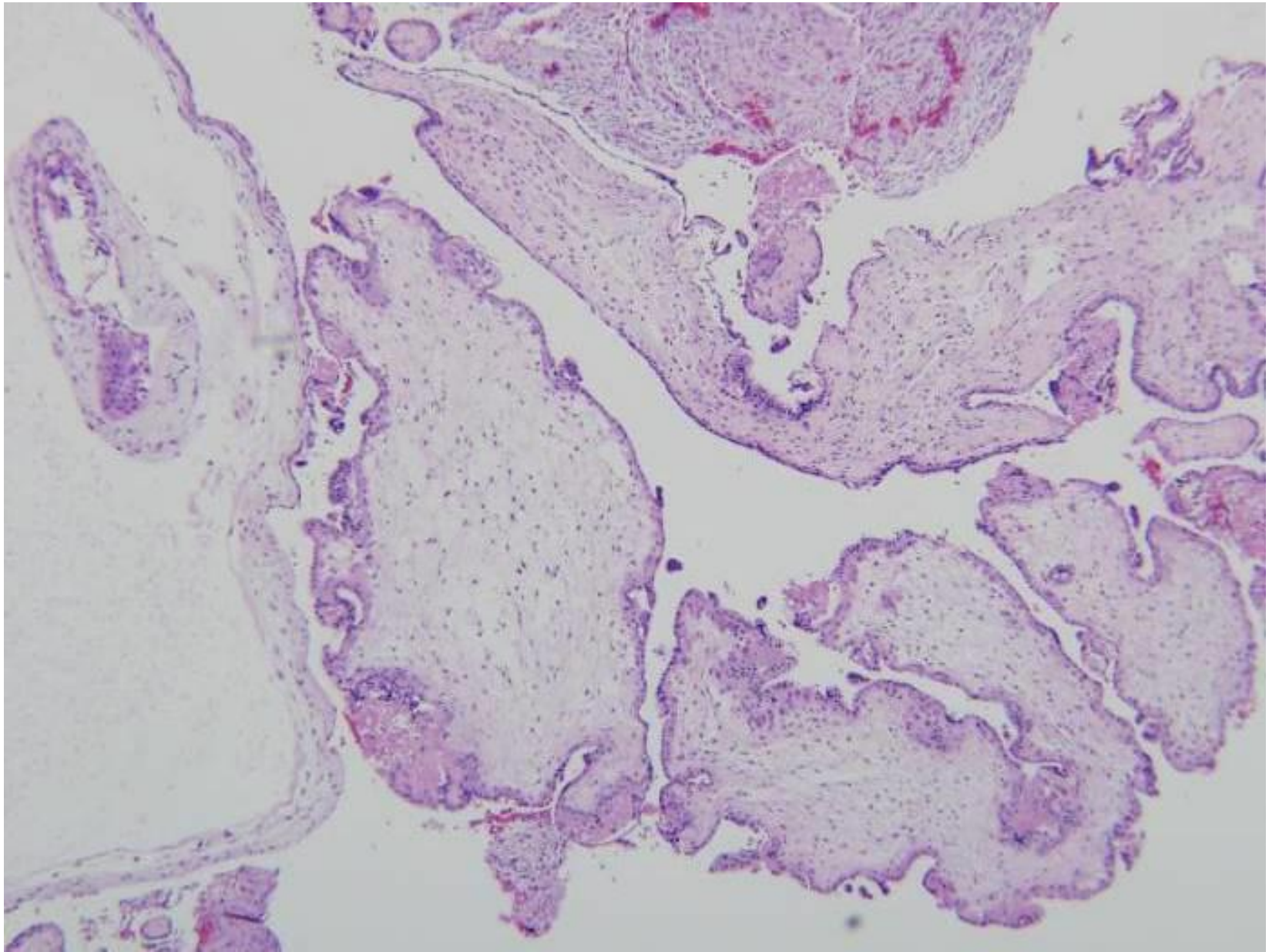
Redline et al, Hum Pathol 1999; 30: 93-100

First trimester: Dysmorphic villi suggestive of chromosomal abnormality (Predictive value positive= 90%)

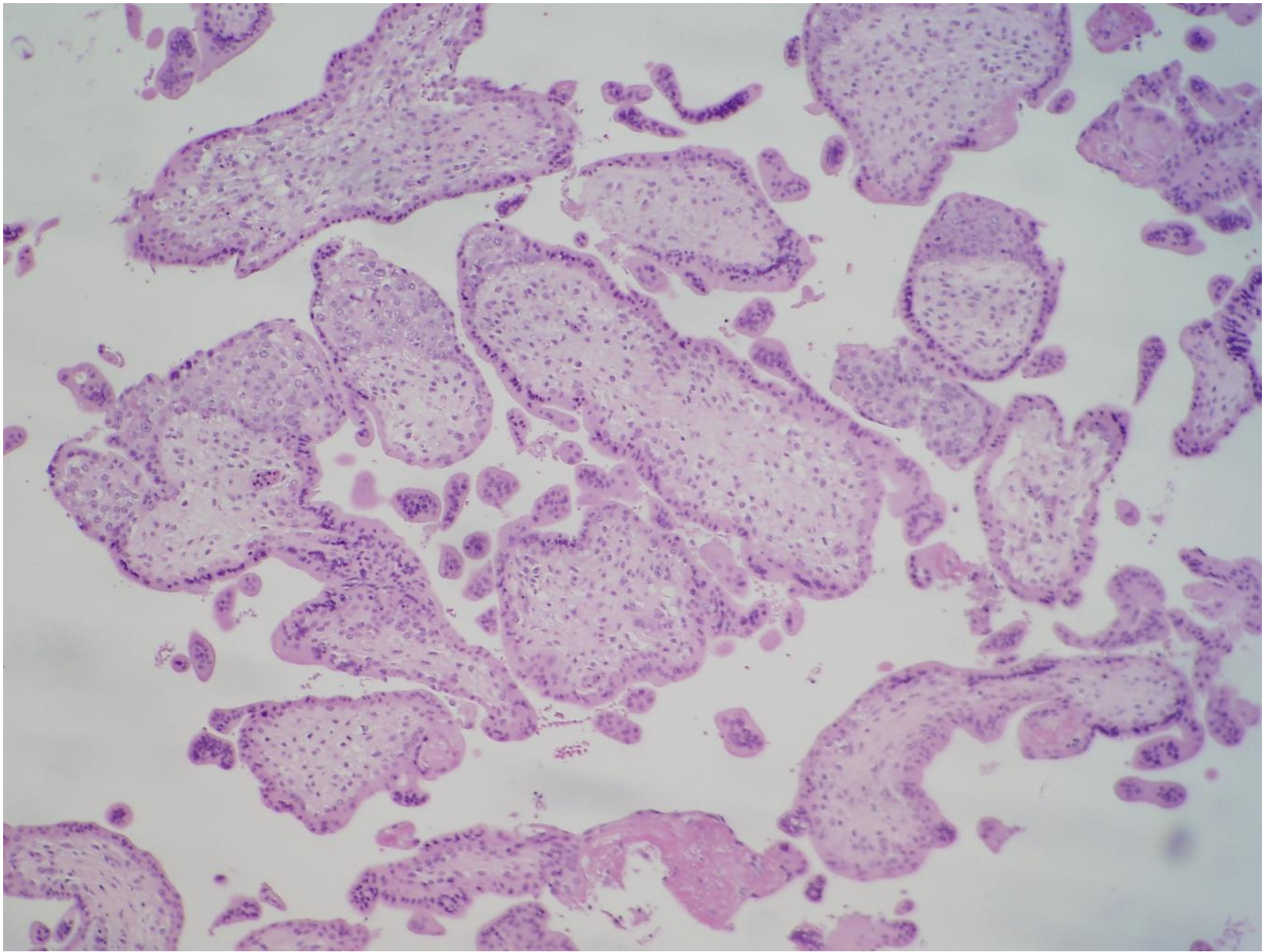




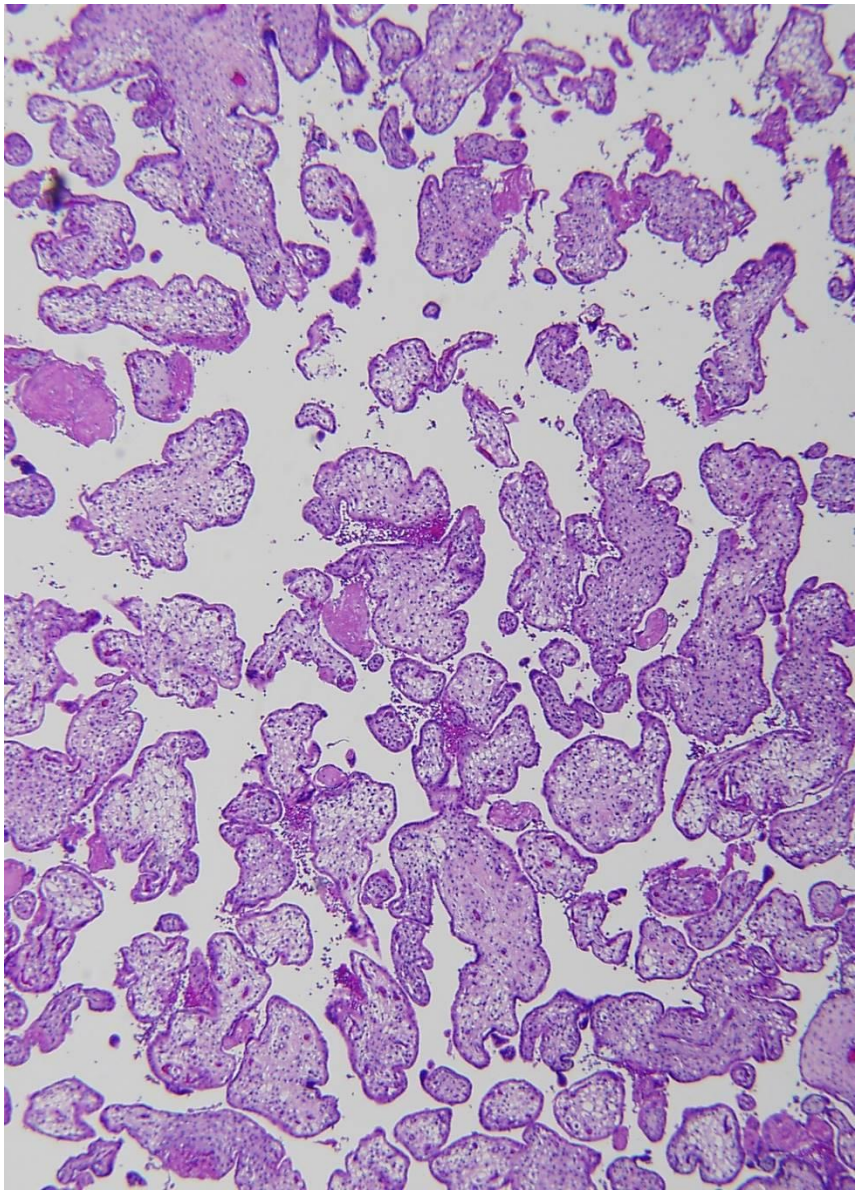
First trimester: Triploidy- hydropic villi/ cisterns, irregular villous contour, trophoblast inclusions

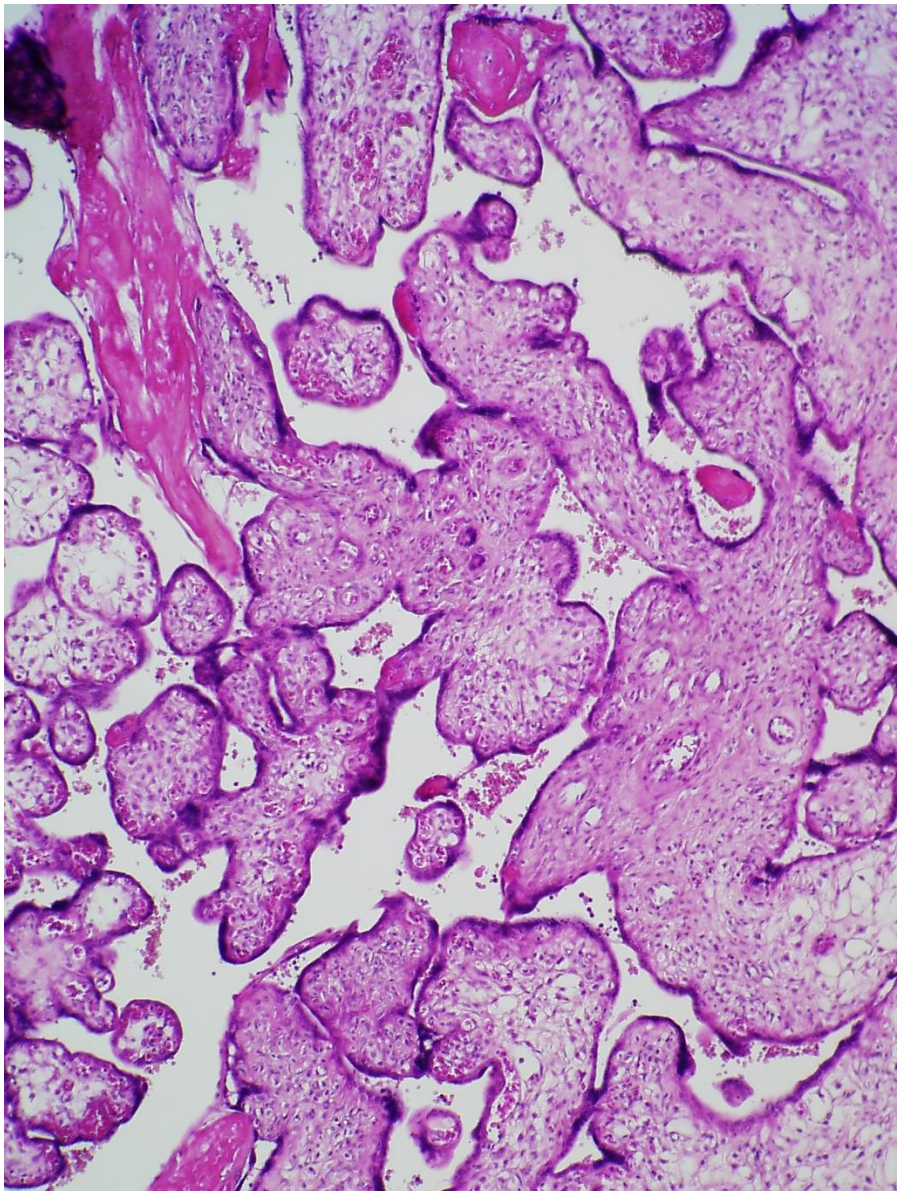


First trimester: monosomy X with syncytial sprouts

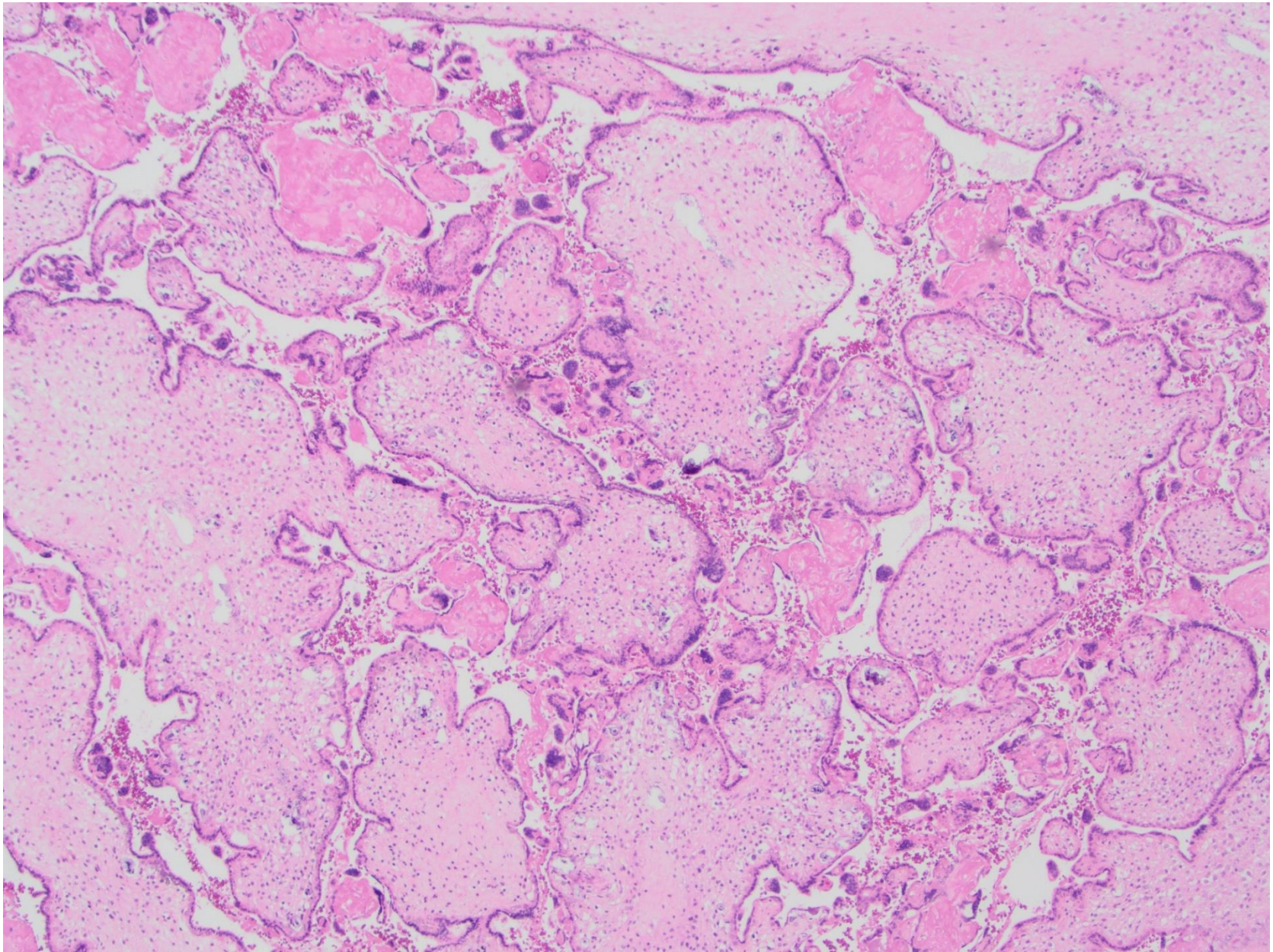


Third trimester: FGR with dysmorphic villi, irregular contour, and trophoblast inclusions

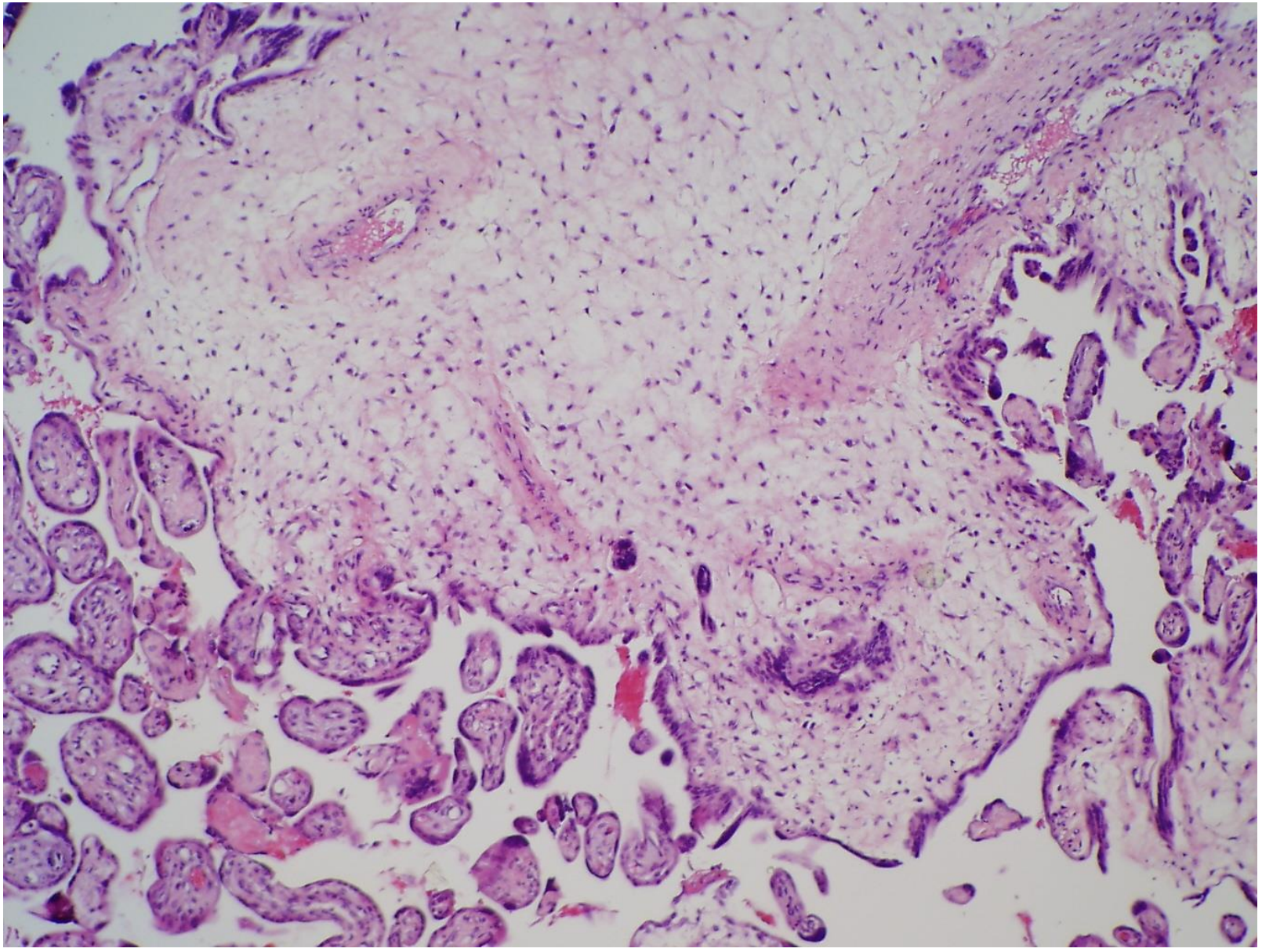




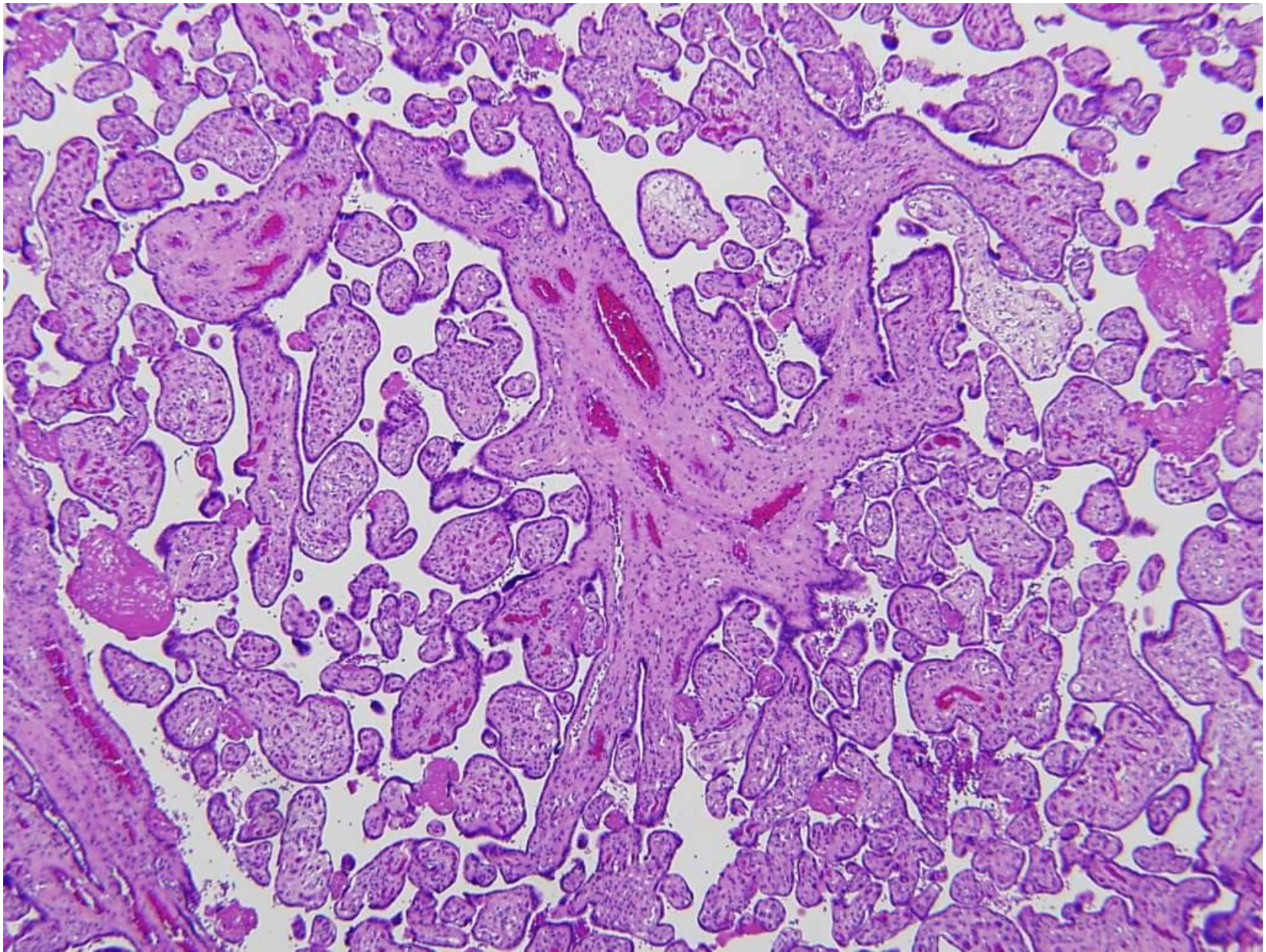
Third trimester: FGR with proximal/ distal villous discordance, irregular villous contour, and increased syncytial knots



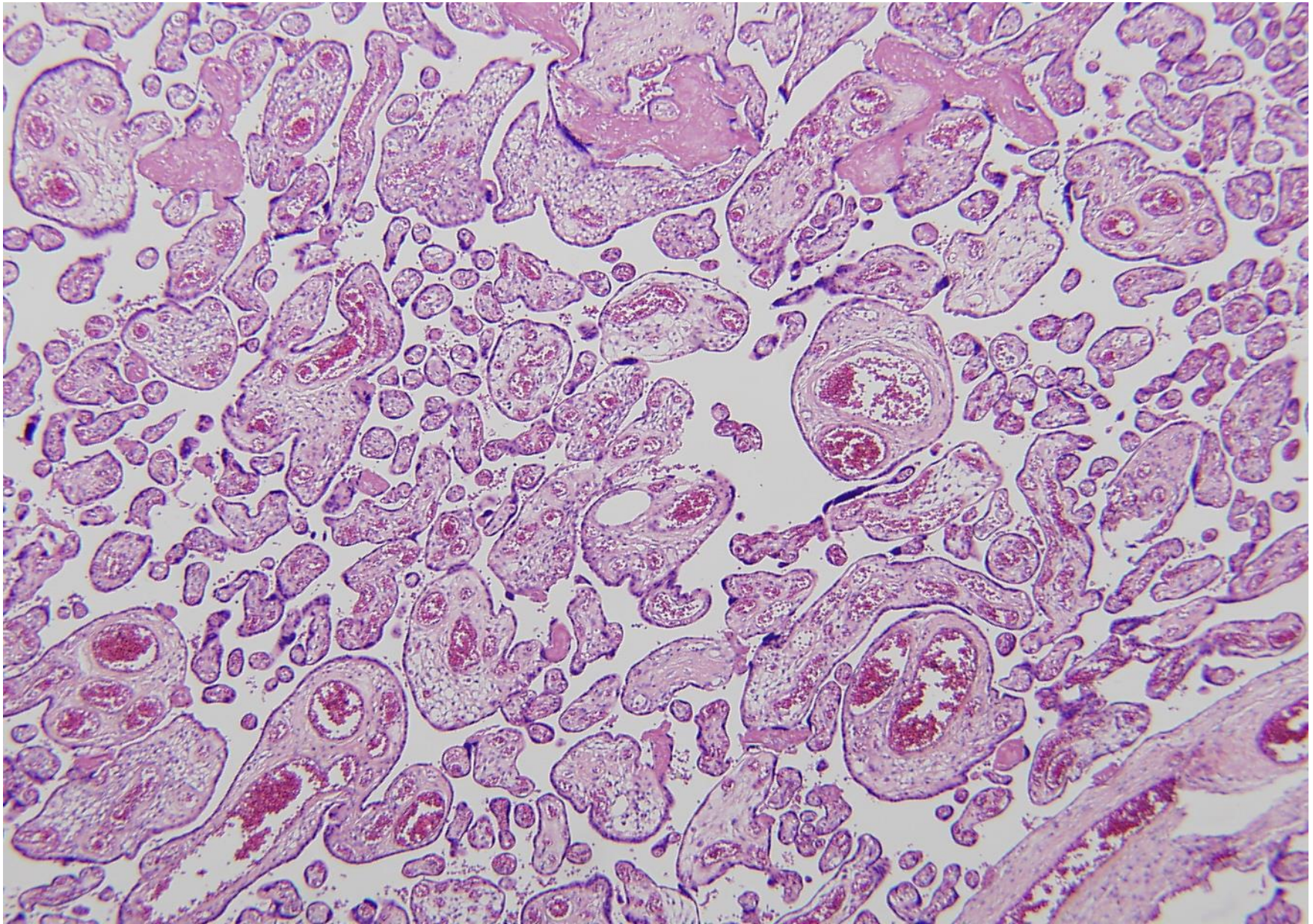
Third trimester: FGR with proximal/ distal villous discordance, stem villous edema, and accelerated villous maturation



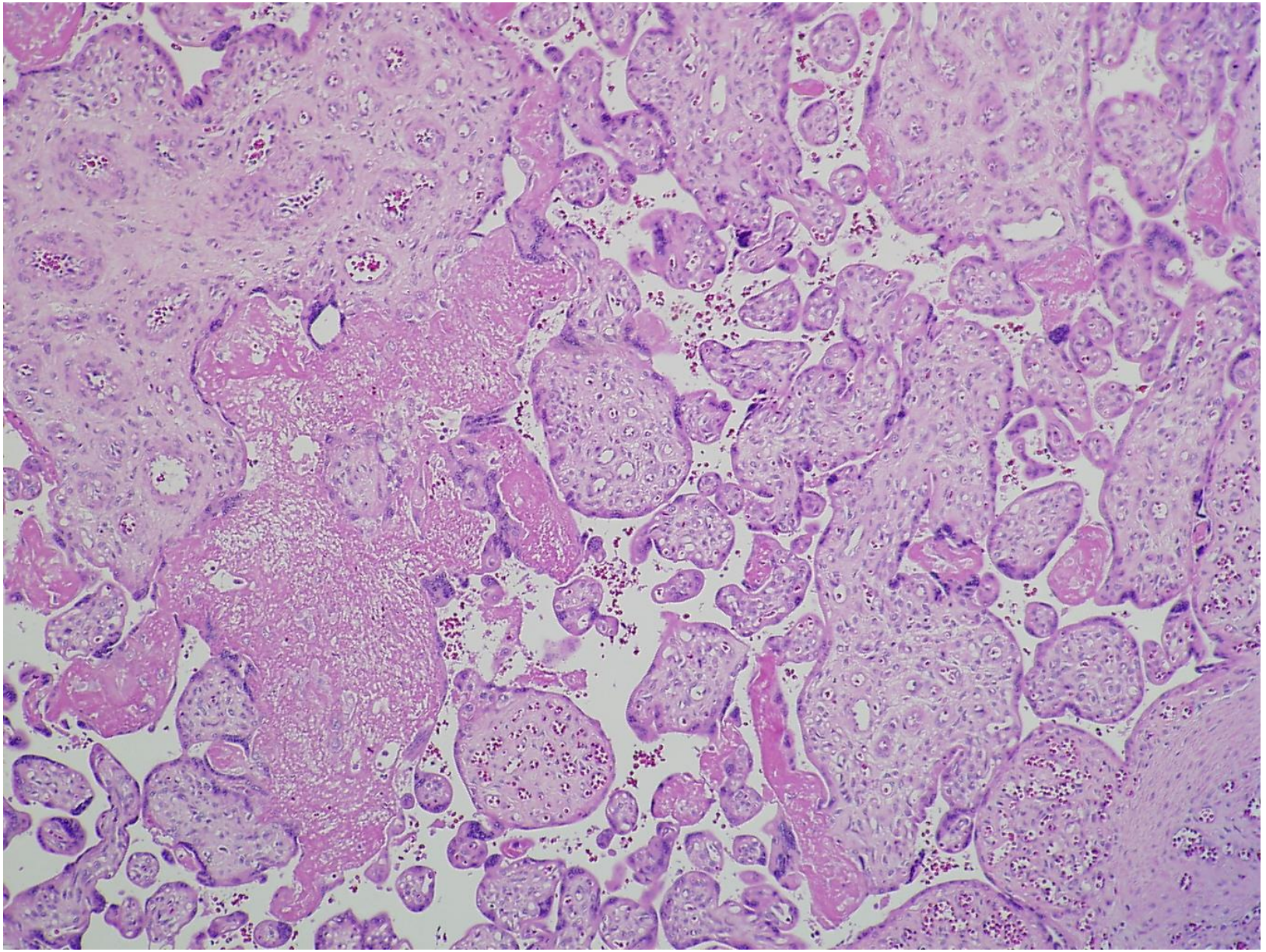
Third trimester: FGR with proximal/ distal villous discordance and delayed villous maturation



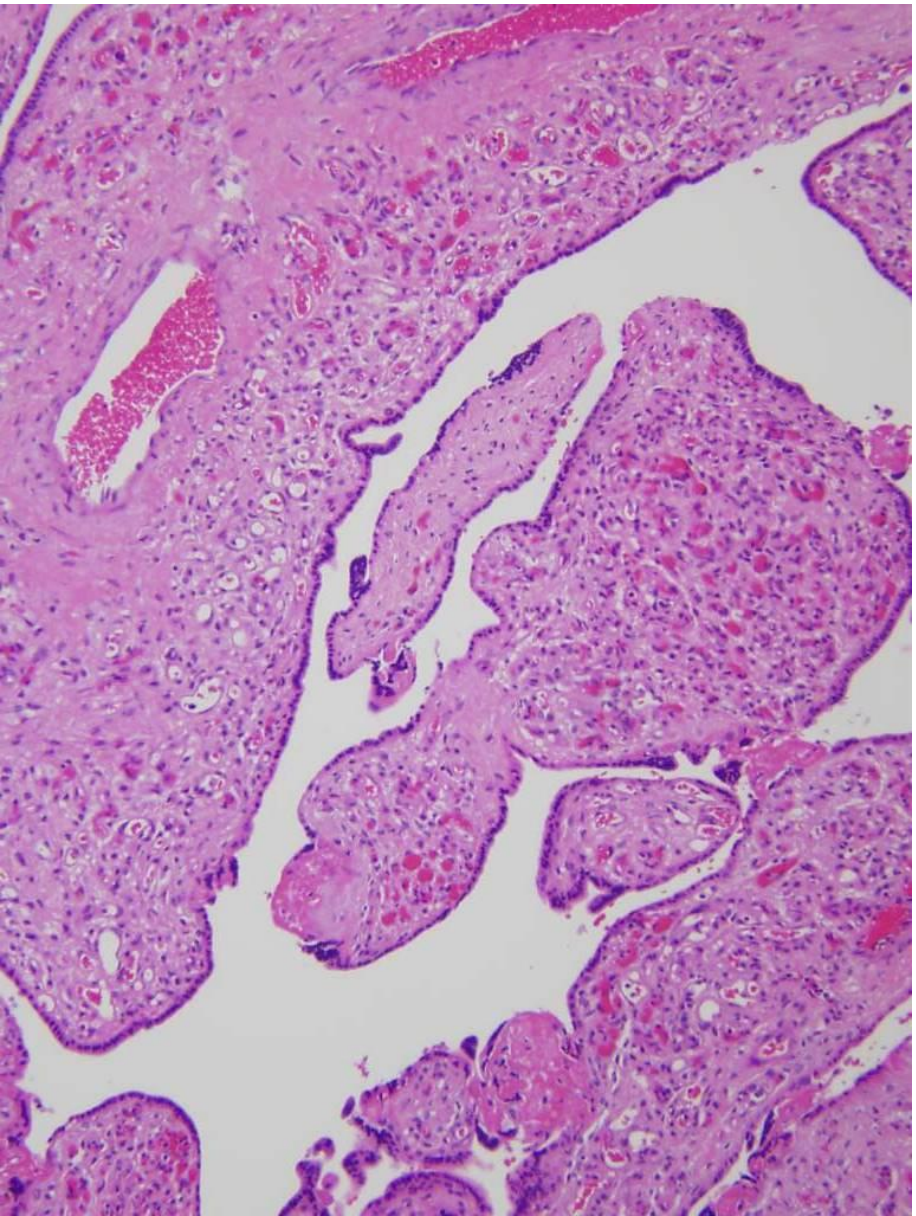
Third trimester: FGR with proximal/ distal villous discordance and nonspecific distal villous edema

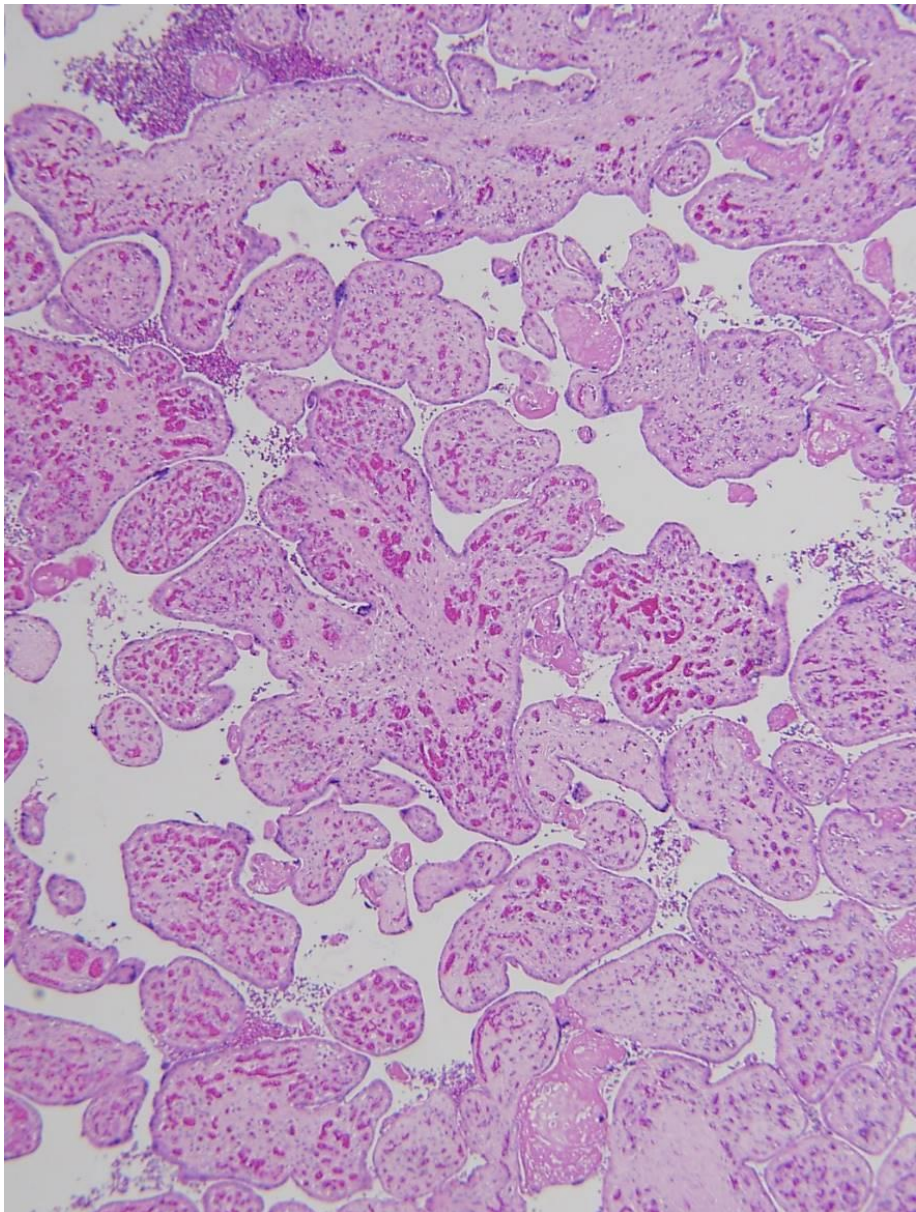


Third trimester: dysmorphic villi, abnormal vascular pattern (large and small vessels)



Third trimester: dysmorphic villi, abnormal vascular pattern
Beckwith-Weidmann syndrome

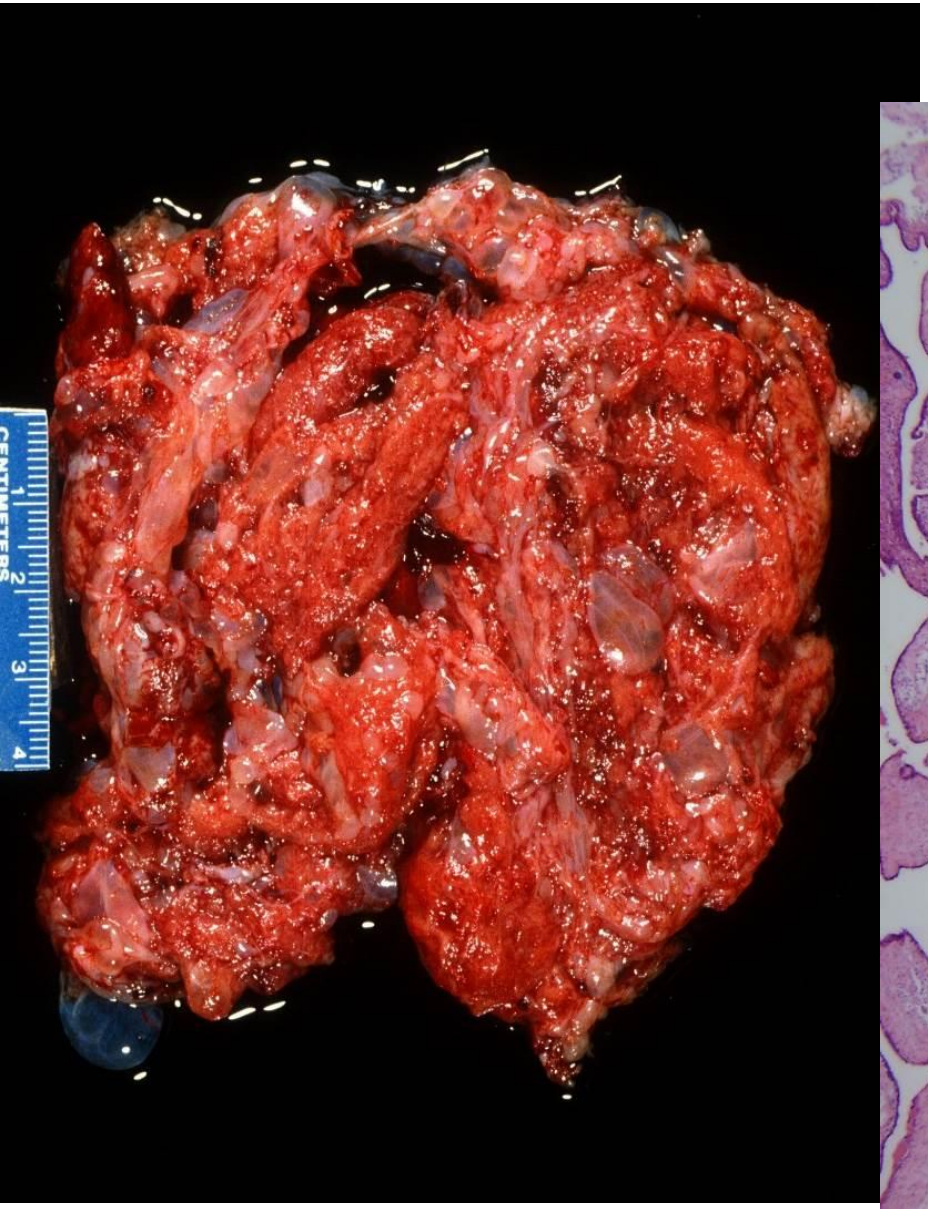


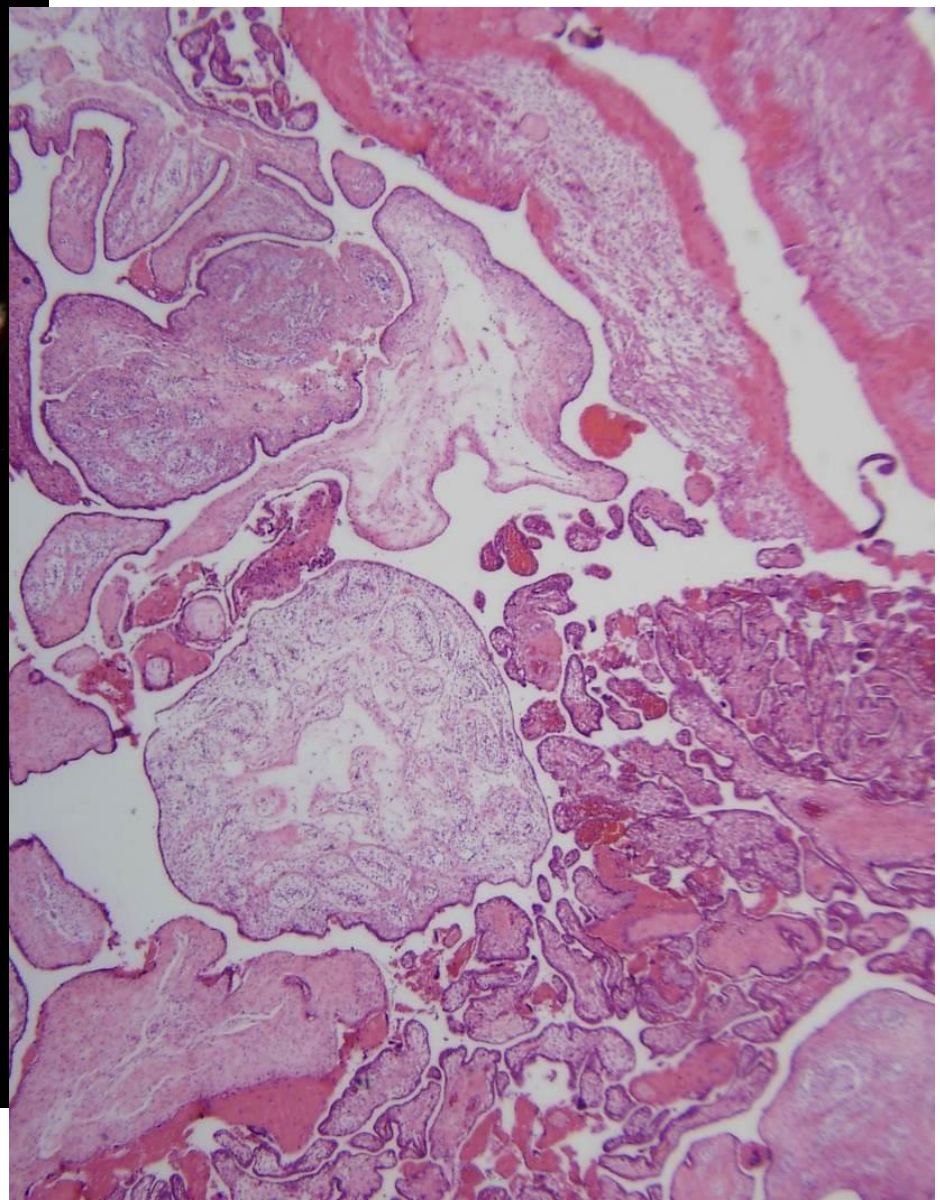


Mesenchymal dysplasia

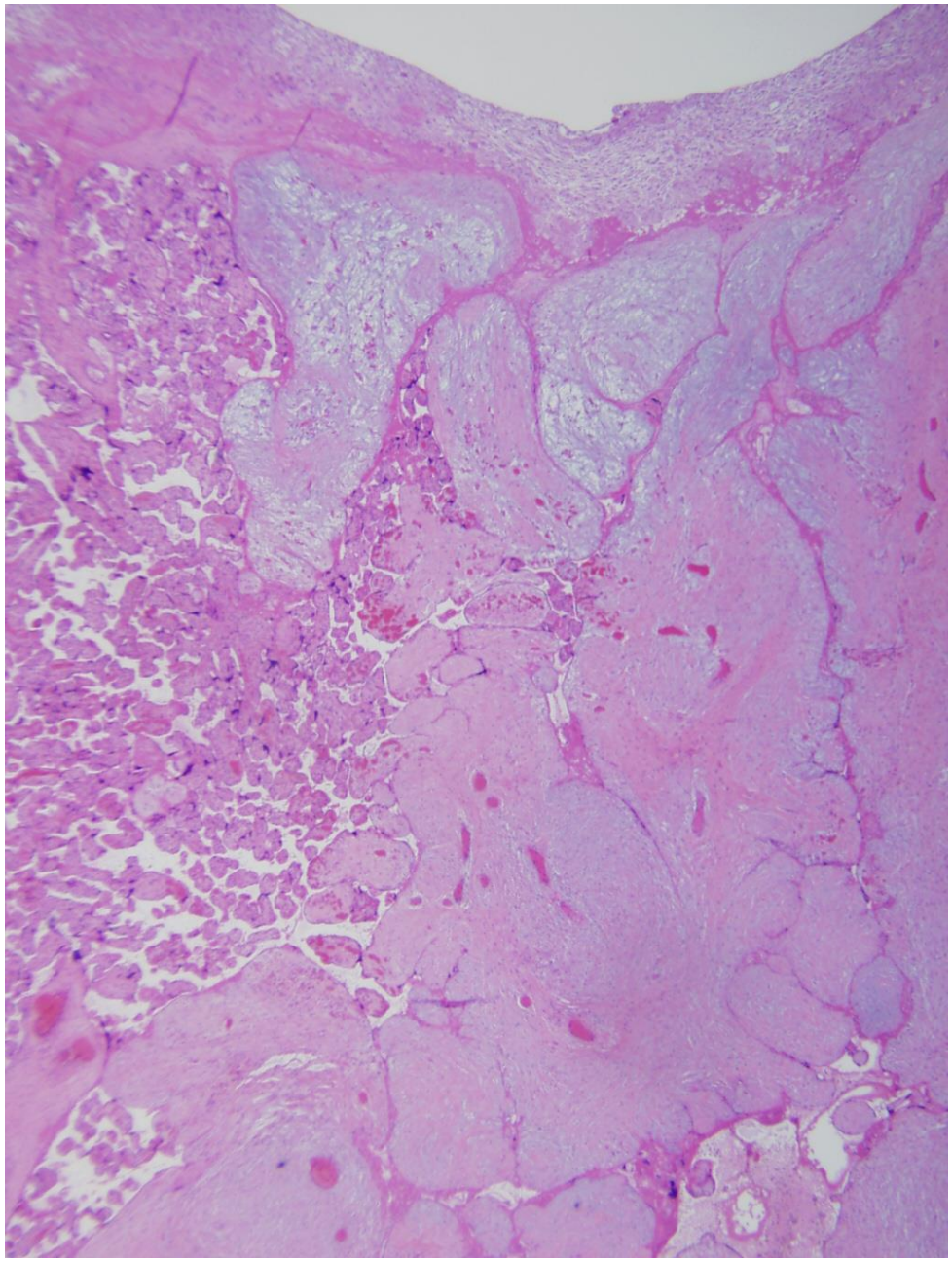
Histology:	abnormal stem villi with marked cystic dilatation, stromal overgrowth, and abnormalities affecting fetal vessels of all sizes (no trophoblast hyperplasia)
Clinical:	Subchorionic cysts after 8 wks with progression
Two types:	<u>80% Androgenic/ Biparental Mosaicism Chimerism (ABMC)</u> - *Diploid (2P: 0M), stromal cells only* <u>20% Beckwith Weidmann syndrome (BWS)</u> - *Chromosome 11p15 abnormalities*
Other	Extraplacental fetal/neonatal tumors - ABMC: Mesenchymal hamartoma of liver - BWS: Wilm’s tumor, Adrenal carcinoma

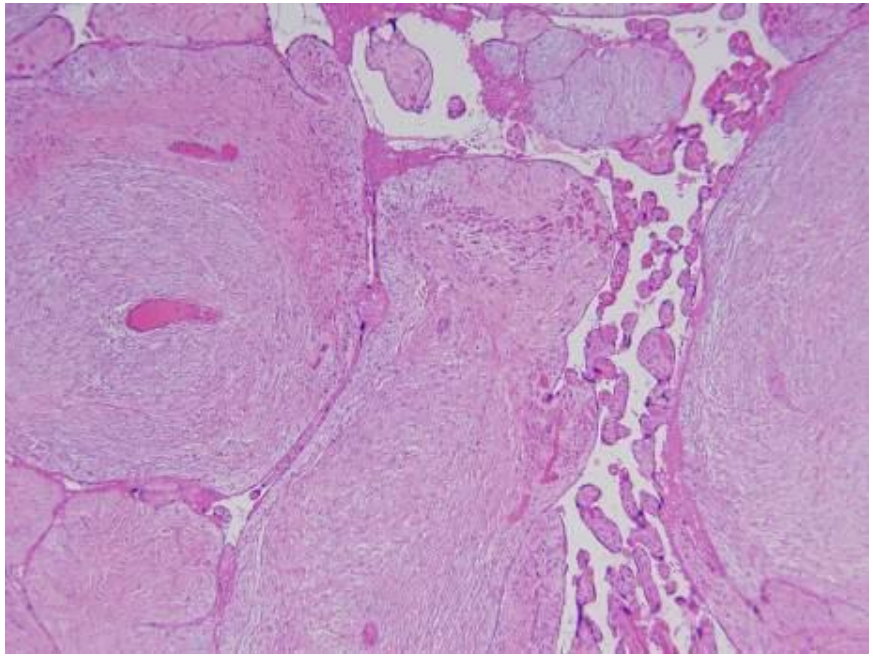
Mesenchymal dysplasia

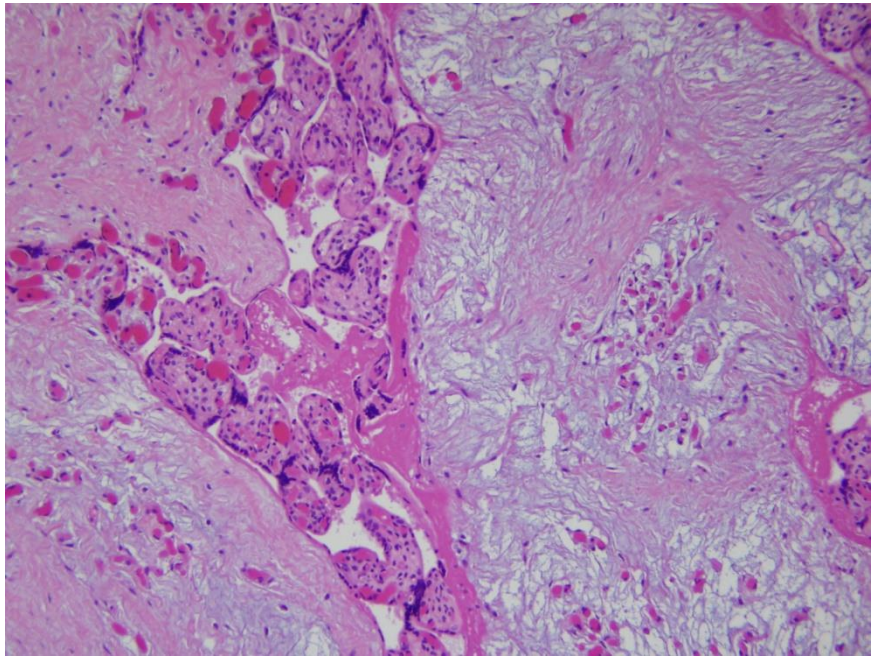


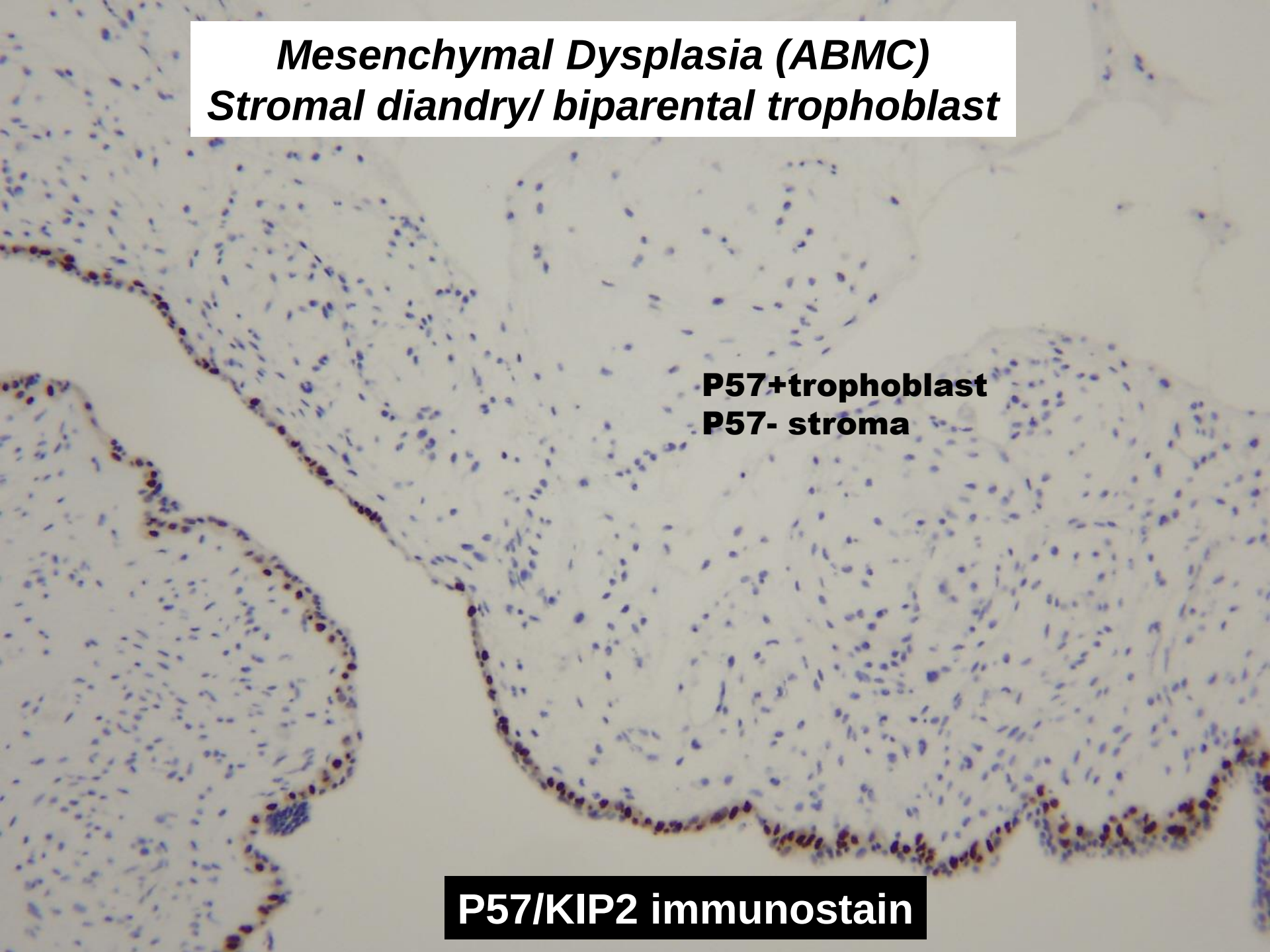


Mesenchymal Dysplasia








Mesenchymal Dysplasia (ABMC)
Stromal diandry/ biparental trophoblast
P57+trophoblast
P57- stroma
P57/KIP2 immunostain