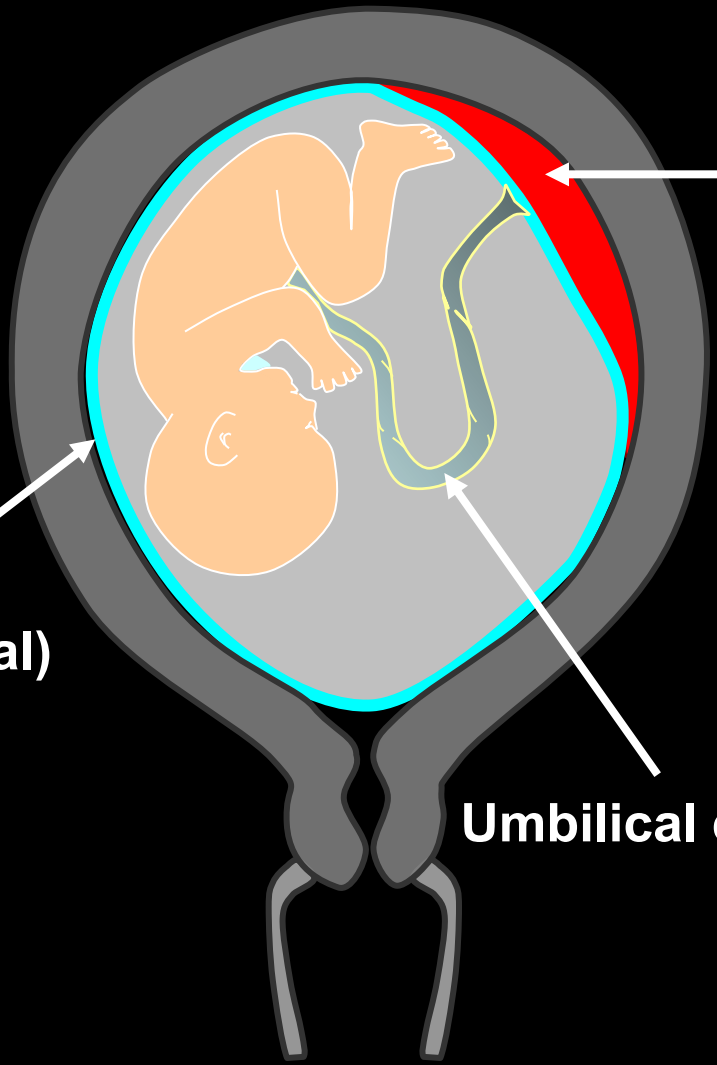
Immune-related Lesions in Preterm Birth

울산의대 서울아산병원 병리과
김종재

Human Placenta

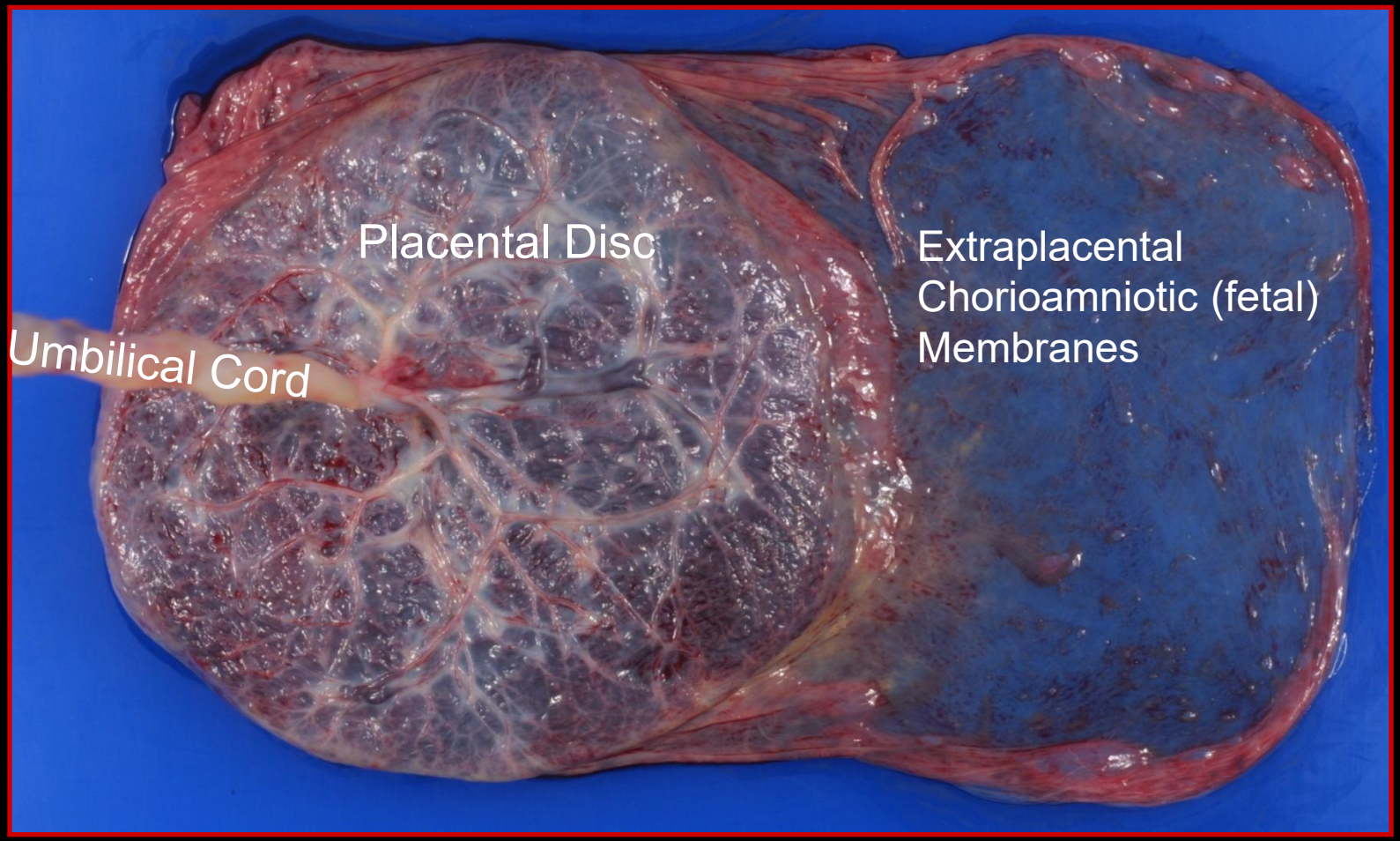


Placental disc
(Villous placenta)

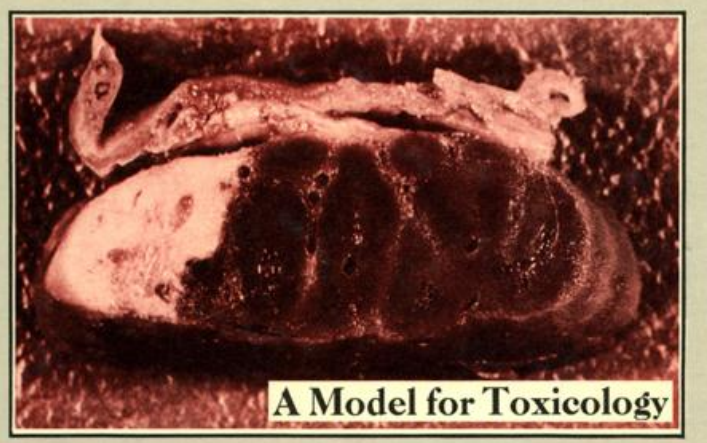
Chorioamniotic (fetal)
membranes

Umbilical cord

Anatomy of the Placenta



Placenta - The Largest Human Biopsy



Rebecca Beaconsfield
& George Birdwood

Pergamon Press

1981

Classification of Preterm Birth

- Gestational age at birth:
  - extremely preterm birth (<28 weeks)
  - moderately preterm birth (28 ~34 weeks)
  - late preterm birth (34~37 weeks)
- Clinical circumstances:
  - spontaneous preterm birth
  - medically indicated preterm birth

Proposed Diagnostic Schema of Placental Pathology

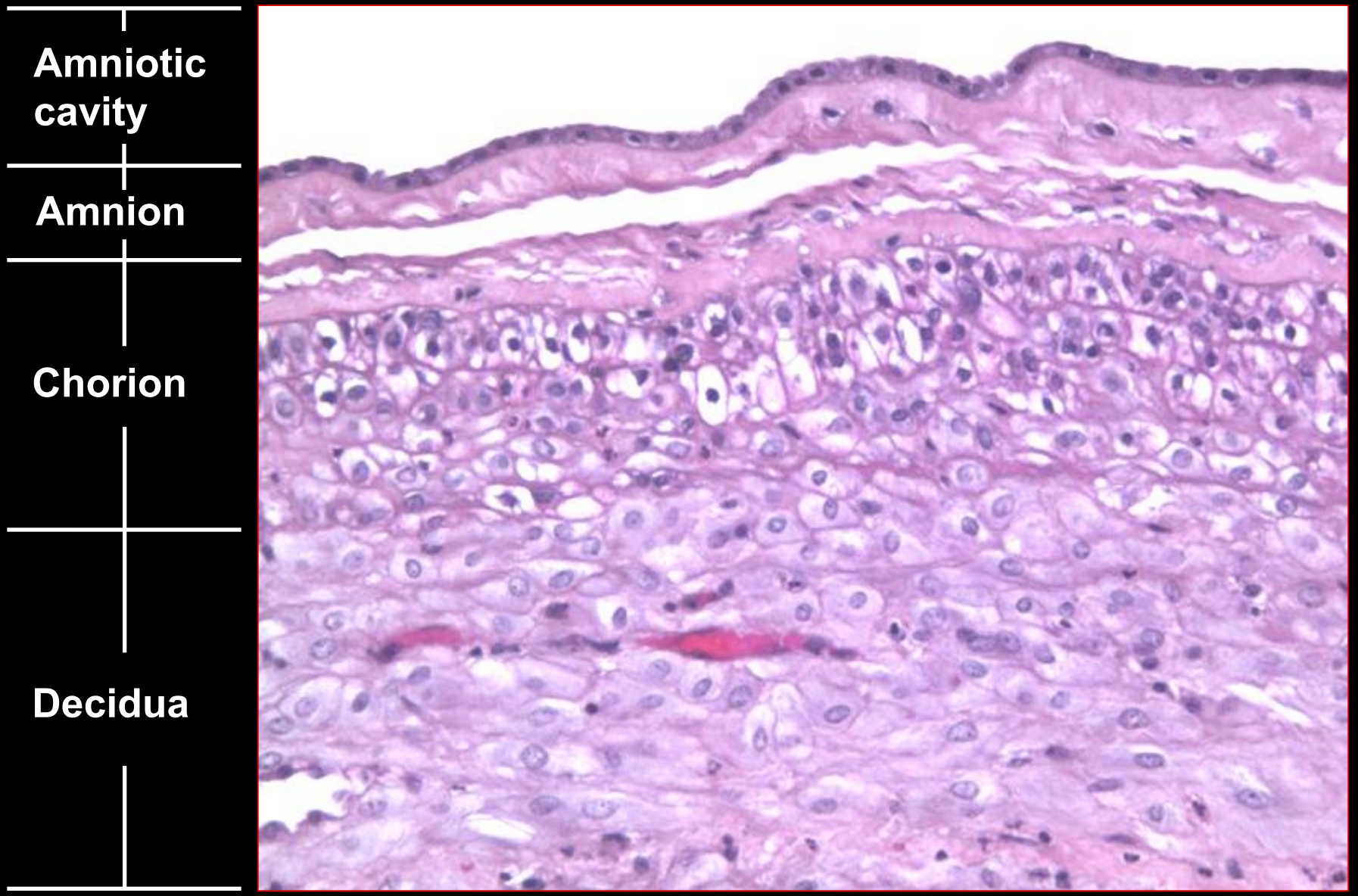
- Perinatal Section, Society for Pediatric Pathology -

- **Amniotic fluid infection**
- **Maternal underperfusion**
- **Fetal vascular thrombo-occlusive disease**
- **Chronic placental inflammation**

Acute Chorioamnionitis

Acute Chorioamnionitis, maternal response

Chorioamniotic Membranes

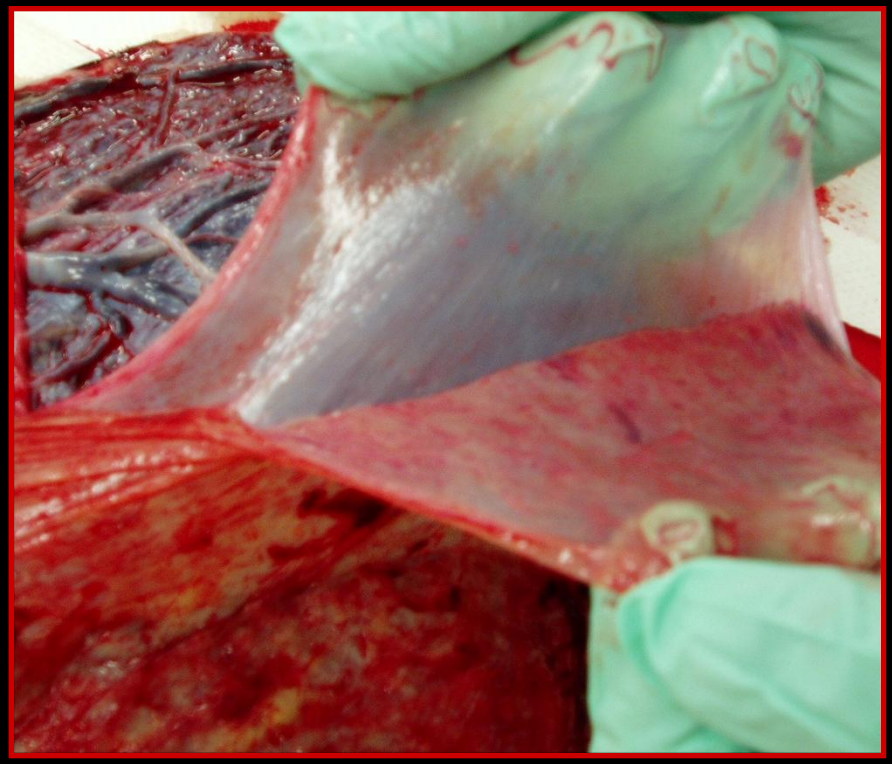


Amnion and Chorion

Amnion

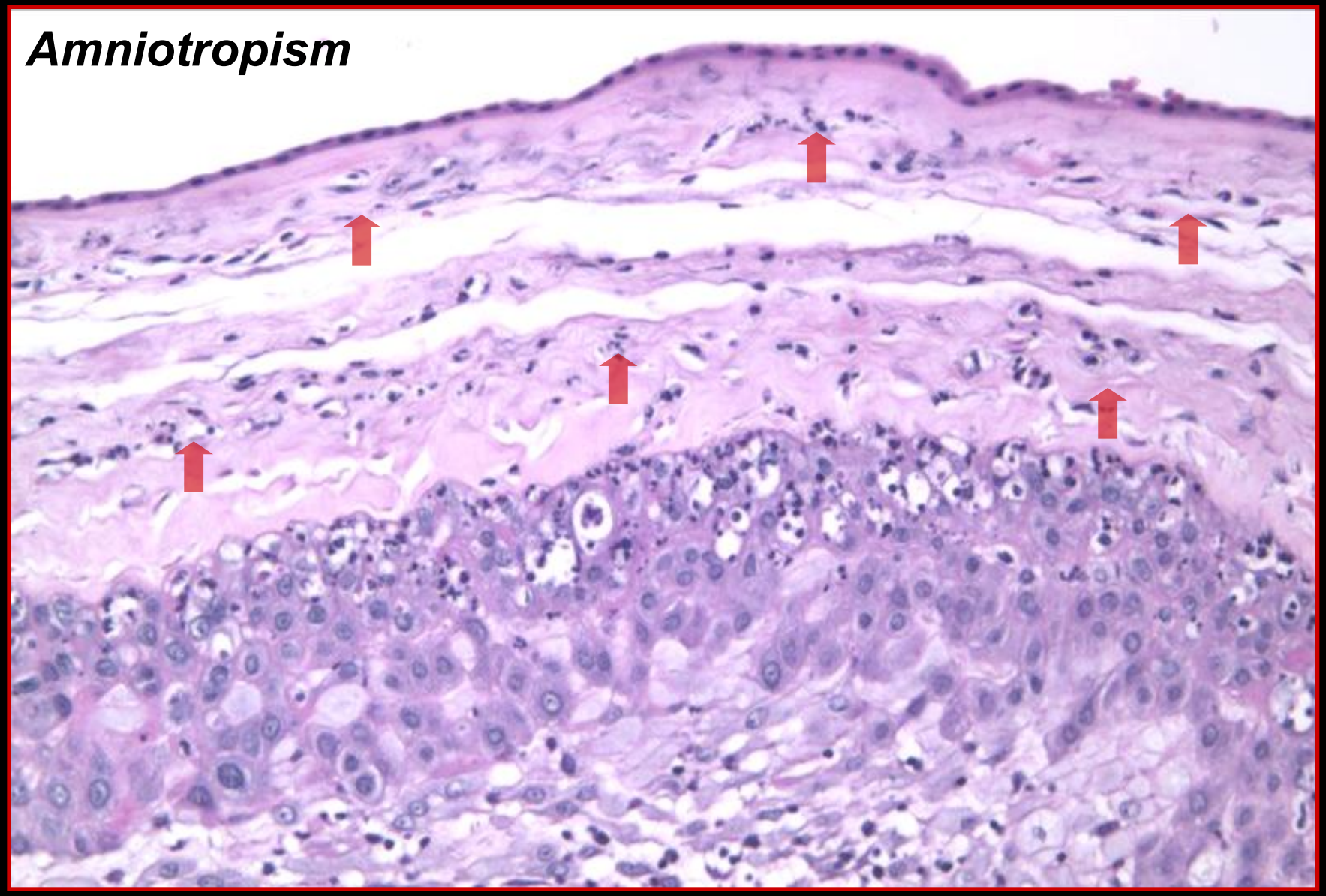
Chorion

Cytokeratin IHC



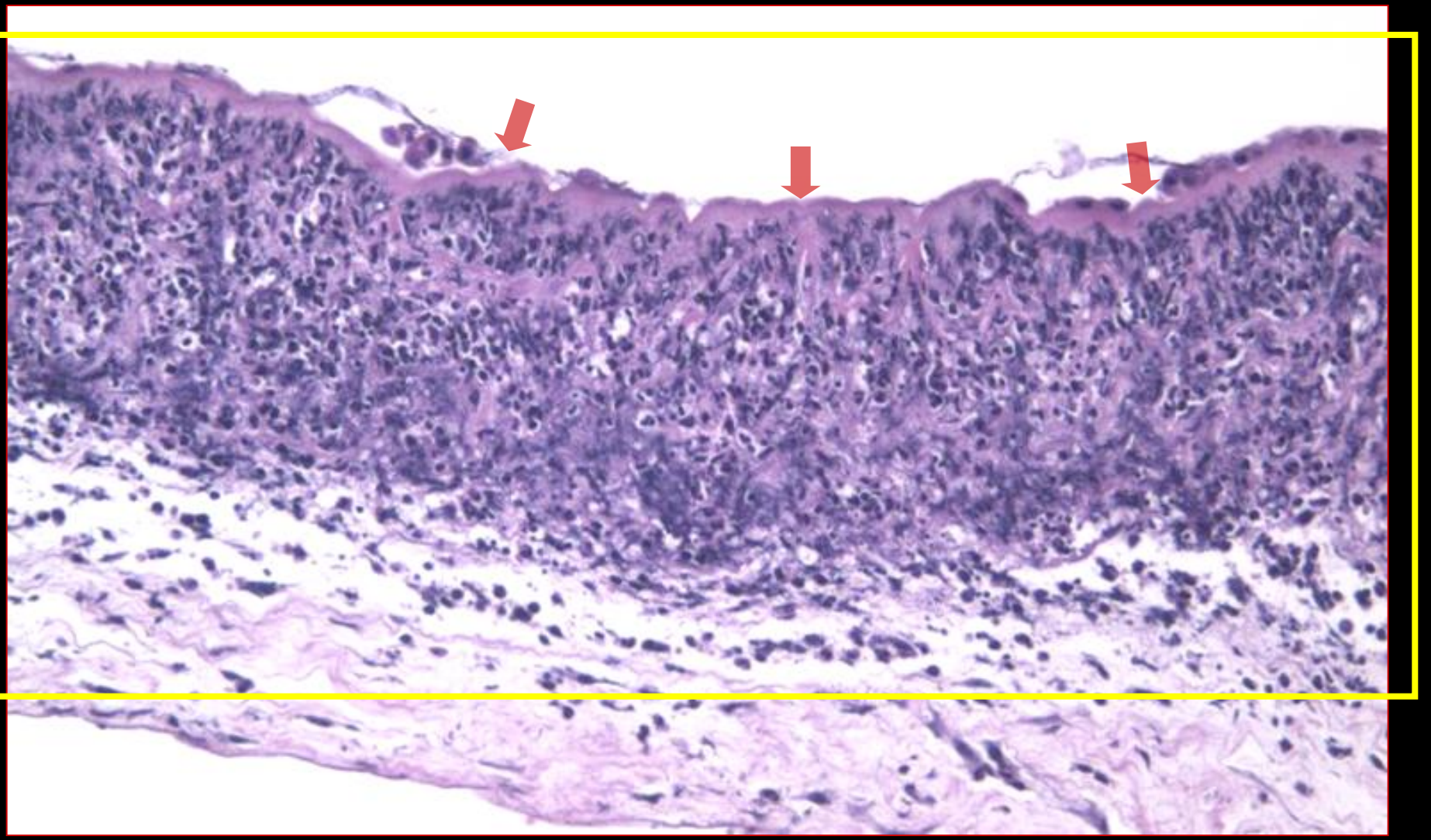
Chorioamnionitis, maternal response

Stage 2 intermediate: acute chorioamnionitis



Chorioamnionitis, maternal response

Stage 3 late: Necrotizing chorioamnionitis

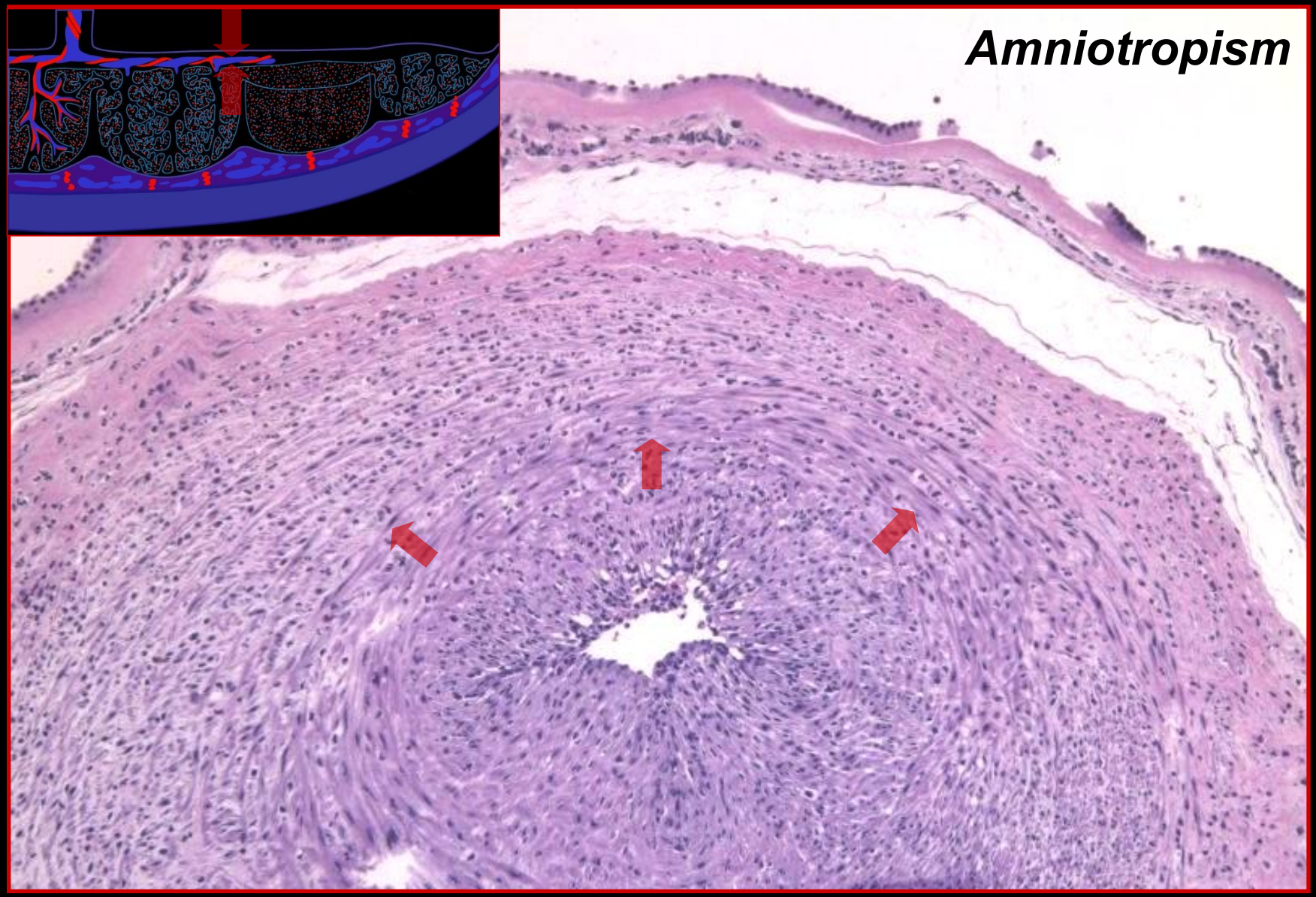


Acute Chorioamnionitis, fetal response

- Chorionic vasculitis
- Umbilical vasculitis (= funisitis)

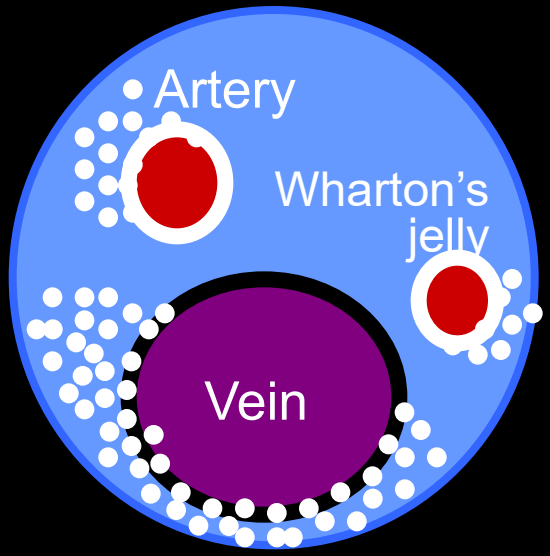
Chorioamnionitis, fetal response

Stage 1 early: chorionic vasculitis



Acute Funisitis

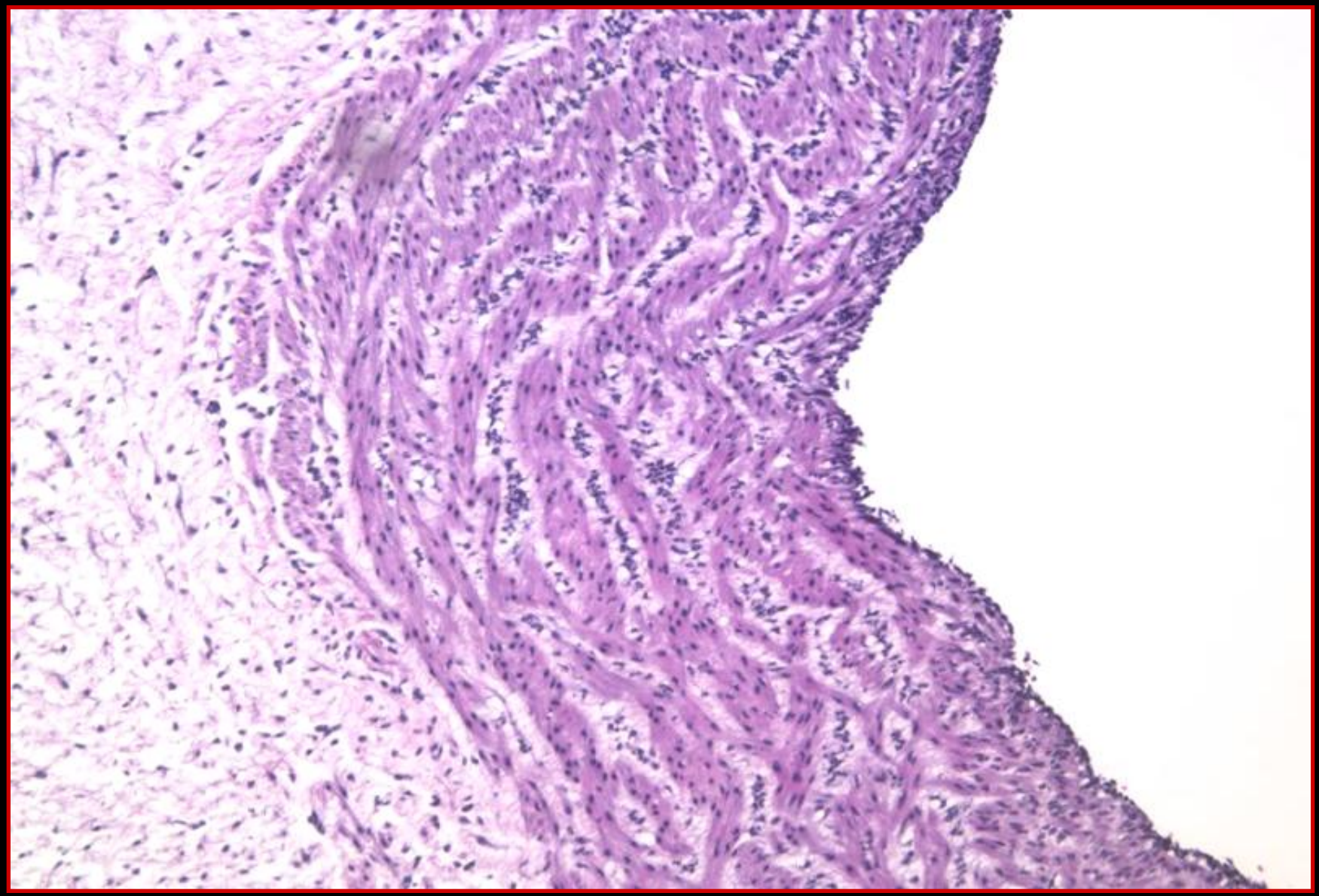
Umbilical Cord



Amniotropism

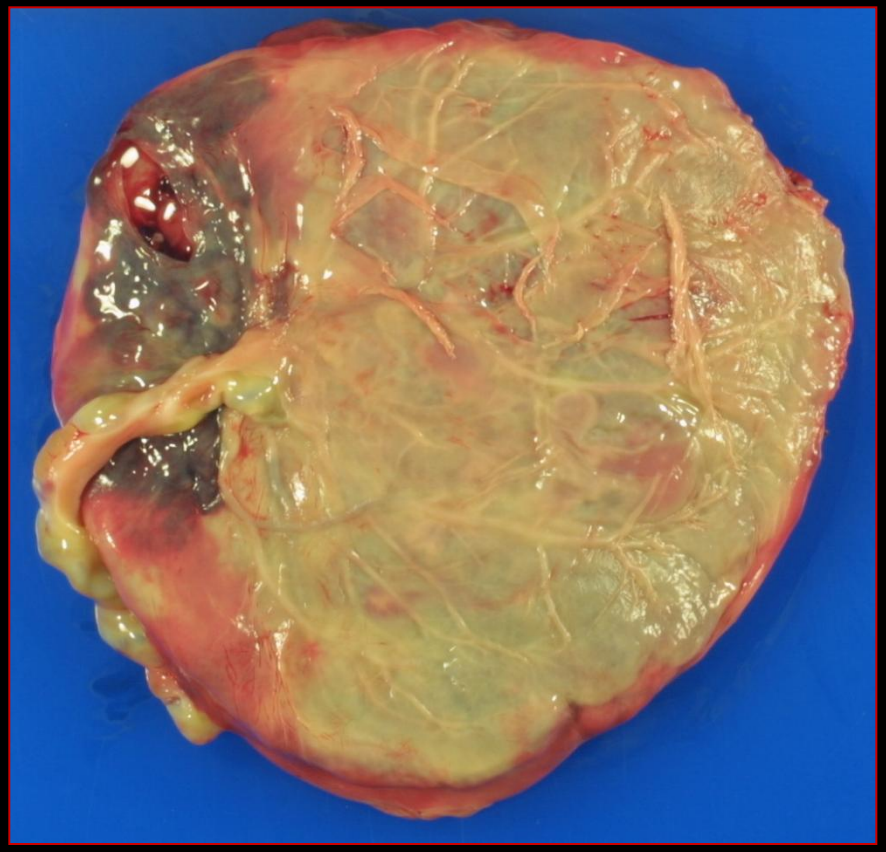
Chorioamnionitis, fetal response

Stage 1 early: umbilical phlebitis



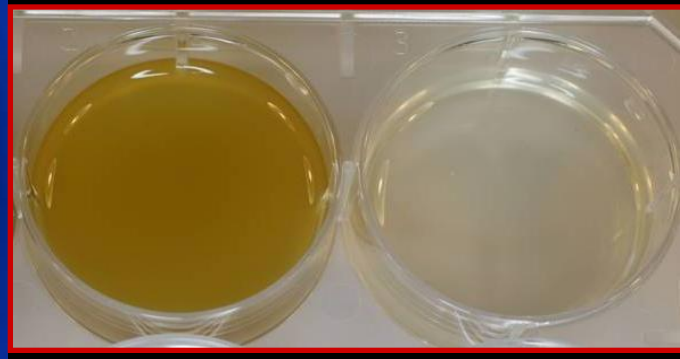
Acute Chorioamnionitis

Normal



Acute Chorioamnionitis

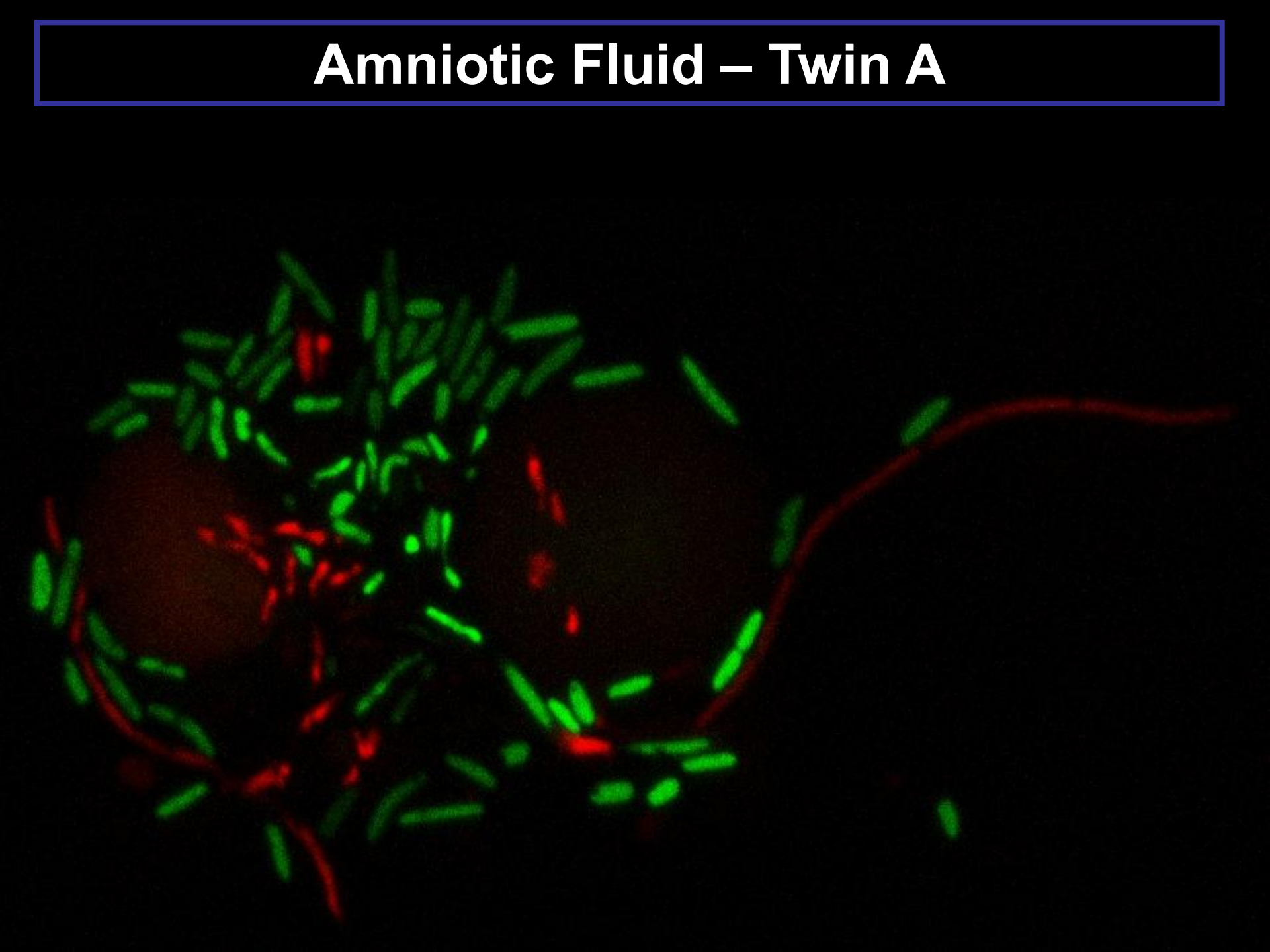
Case HPL5507 (G.A. 25 weeks)



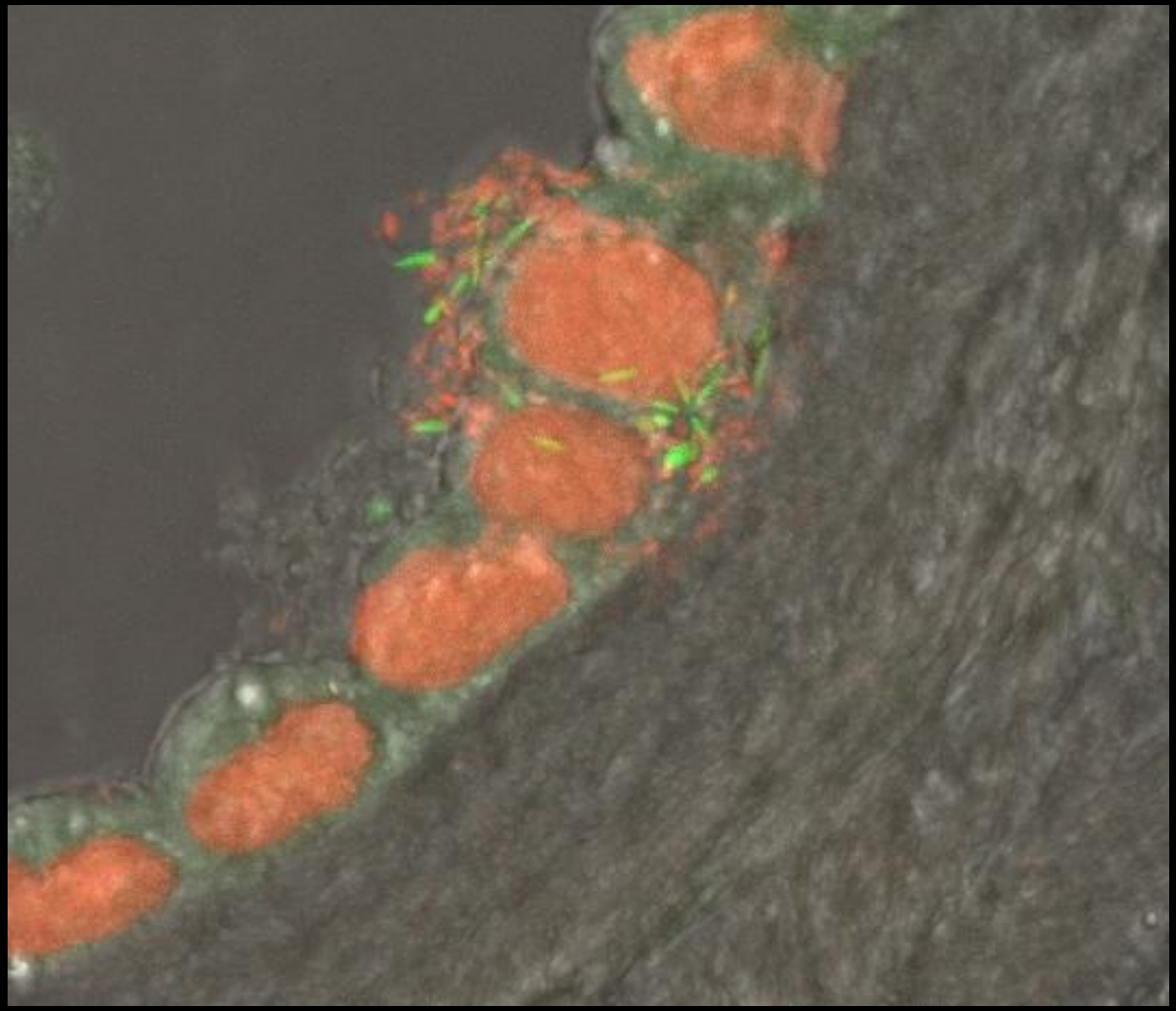
Twin A Twin B

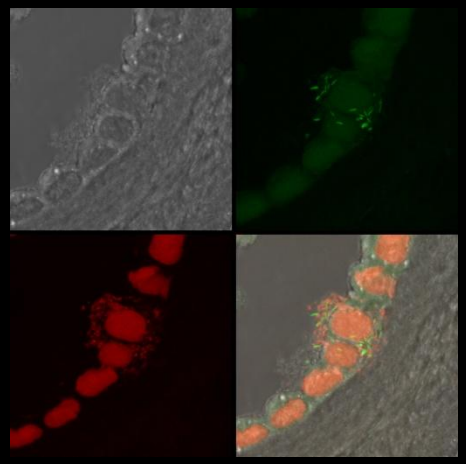
Amniotic Fluid

Amniotic Fluid – Twin A

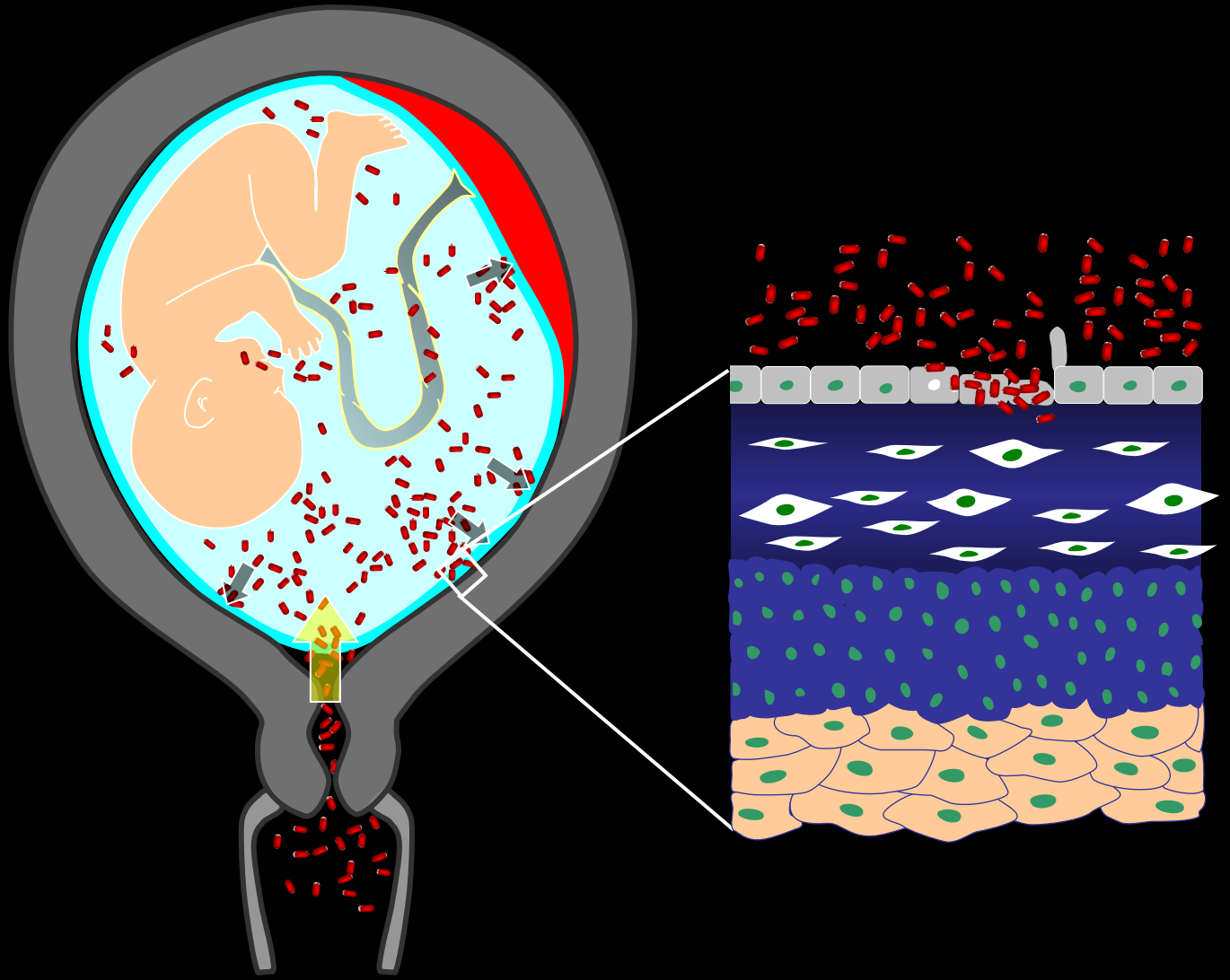


Amnion Epithelial Cells: Twin A



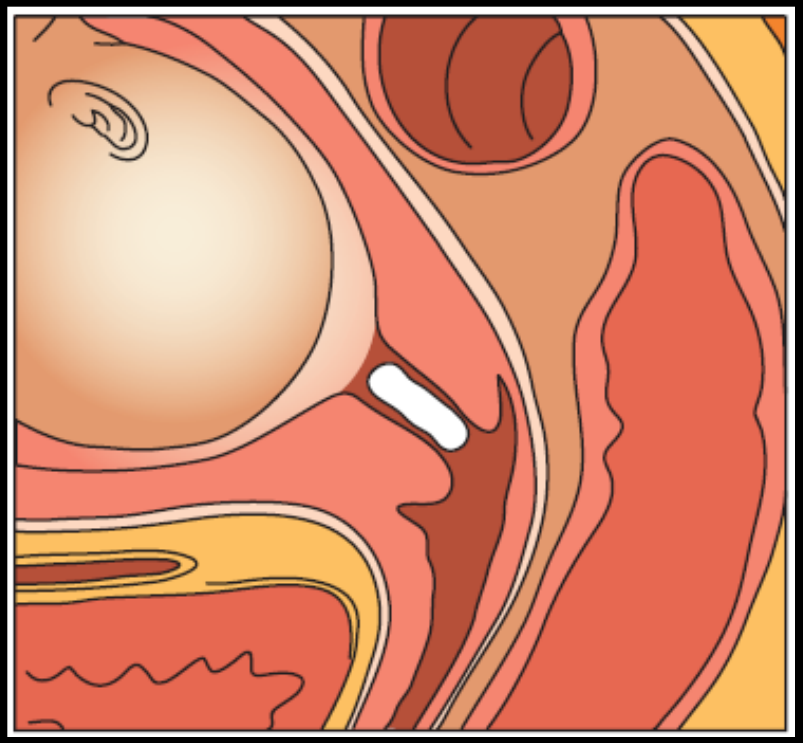


Progression of MIAC



MIAC: Microbial Invasion of the Amniotic Cavity

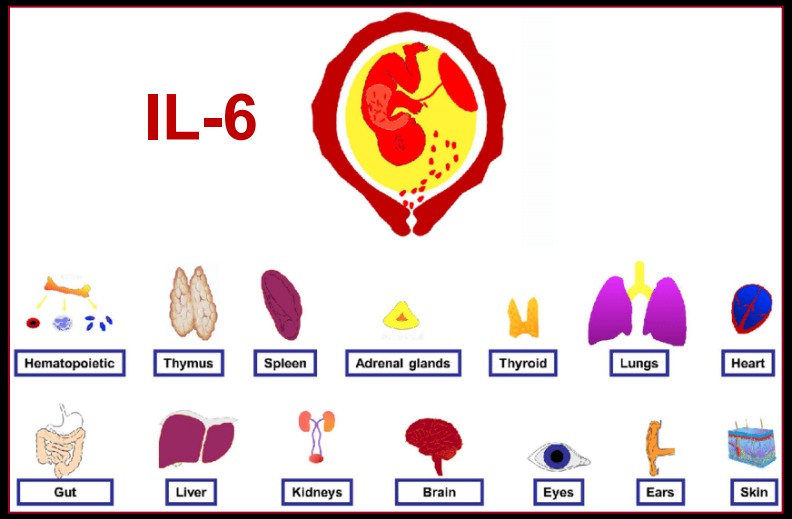
Immunologic Barrier: Cervix



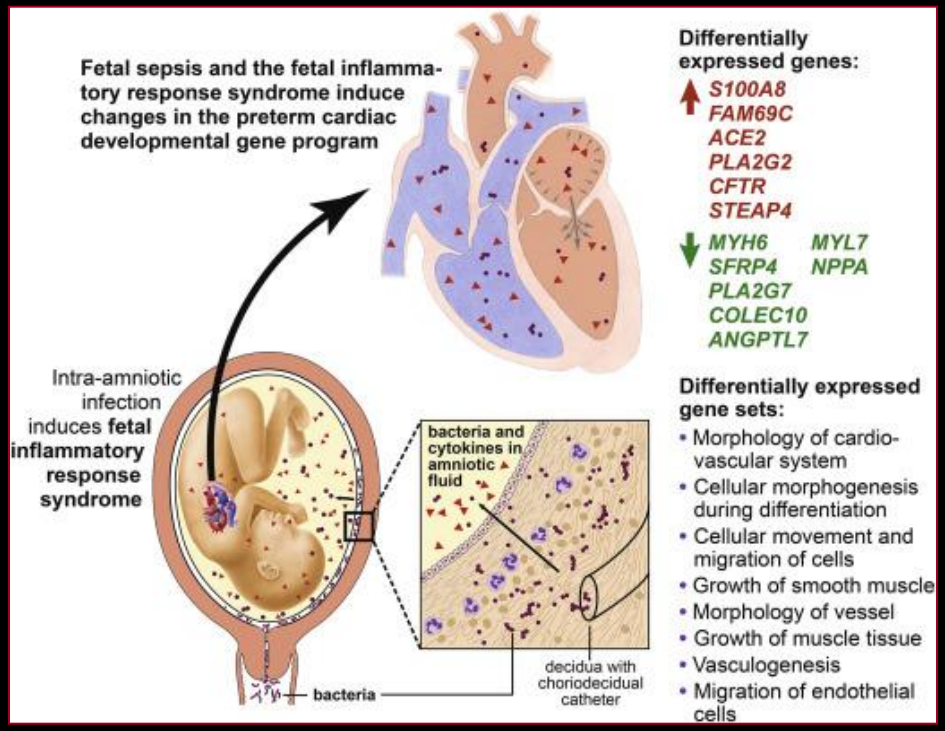
Evidence of cardiac involvement in the fetal inflammatory response syndrome: disruption of gene networks programming cardiac development in nonhuman primates. Mitchell et al. AJOG 2018:218(4):P438.E1-438.E16

Background

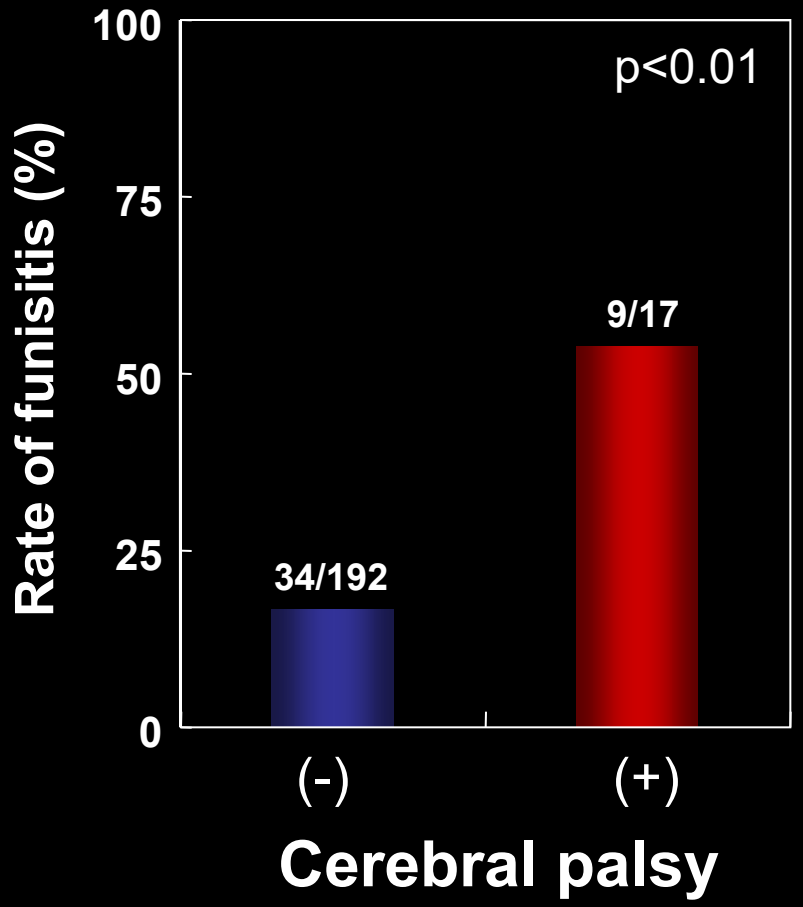
Most early preterm births are associated with intraamniotic infection and inflammation, which can lead to systemic inflammation in the fetus. The fetal inflammatory response syndrome (FIRS) describes elevations in the fetal interleukin-6 level, which is a marker for inflammation and fetal organ injury. An understanding of the effects of inflammation on fetal cardiac development may lead to insight into the fetal origins of adult cardiovascular disease.



Gotsch et a. Fetal Inflammatory Response Syndrome. Clinical Obstetrics and Gynecology 2007:50:652-683



Funisitis and Cerebral Palsy



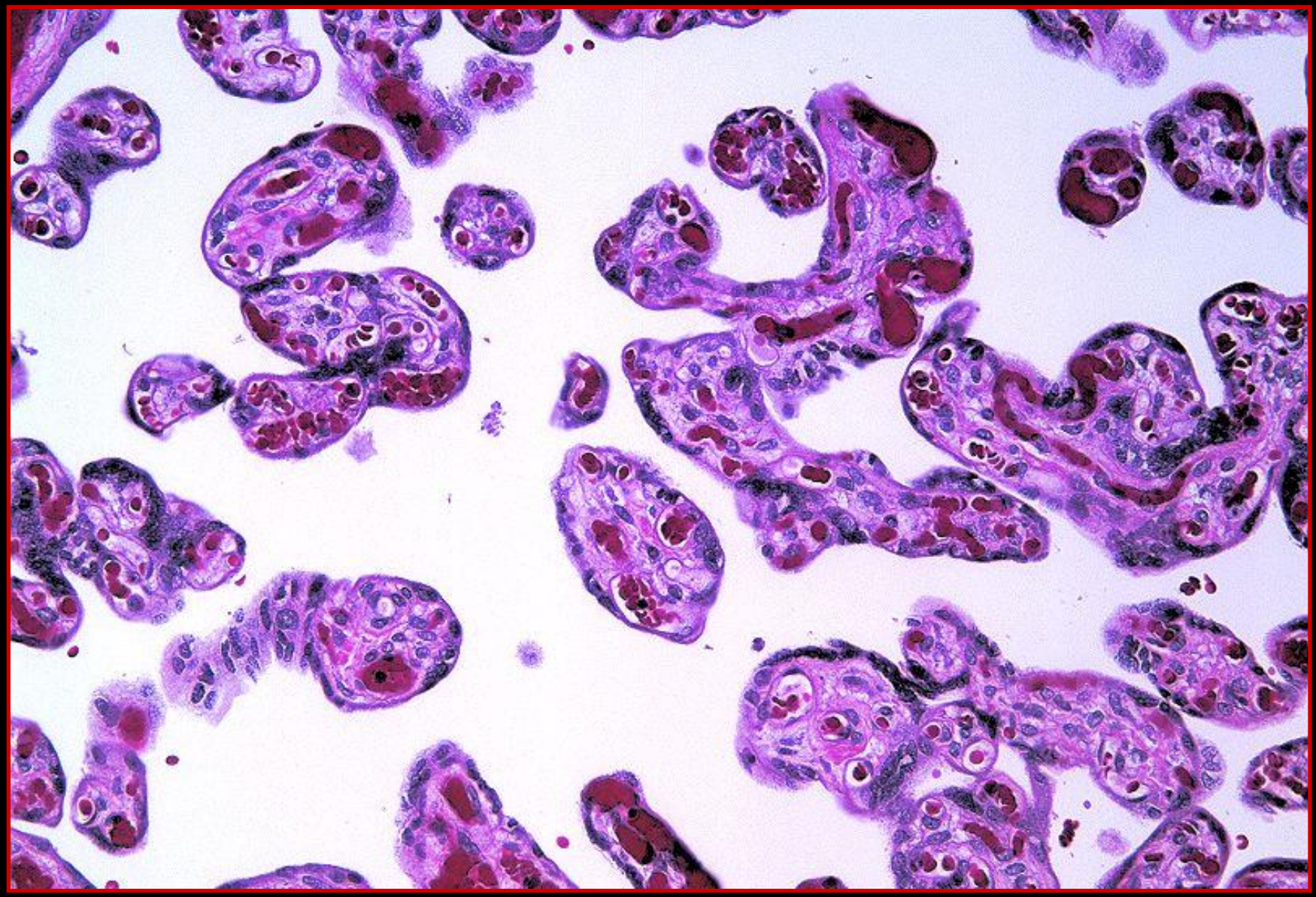
Yoon BH et al. Am J Obstet Gynecol 2000;182:675

Chronic Placental Inflammation

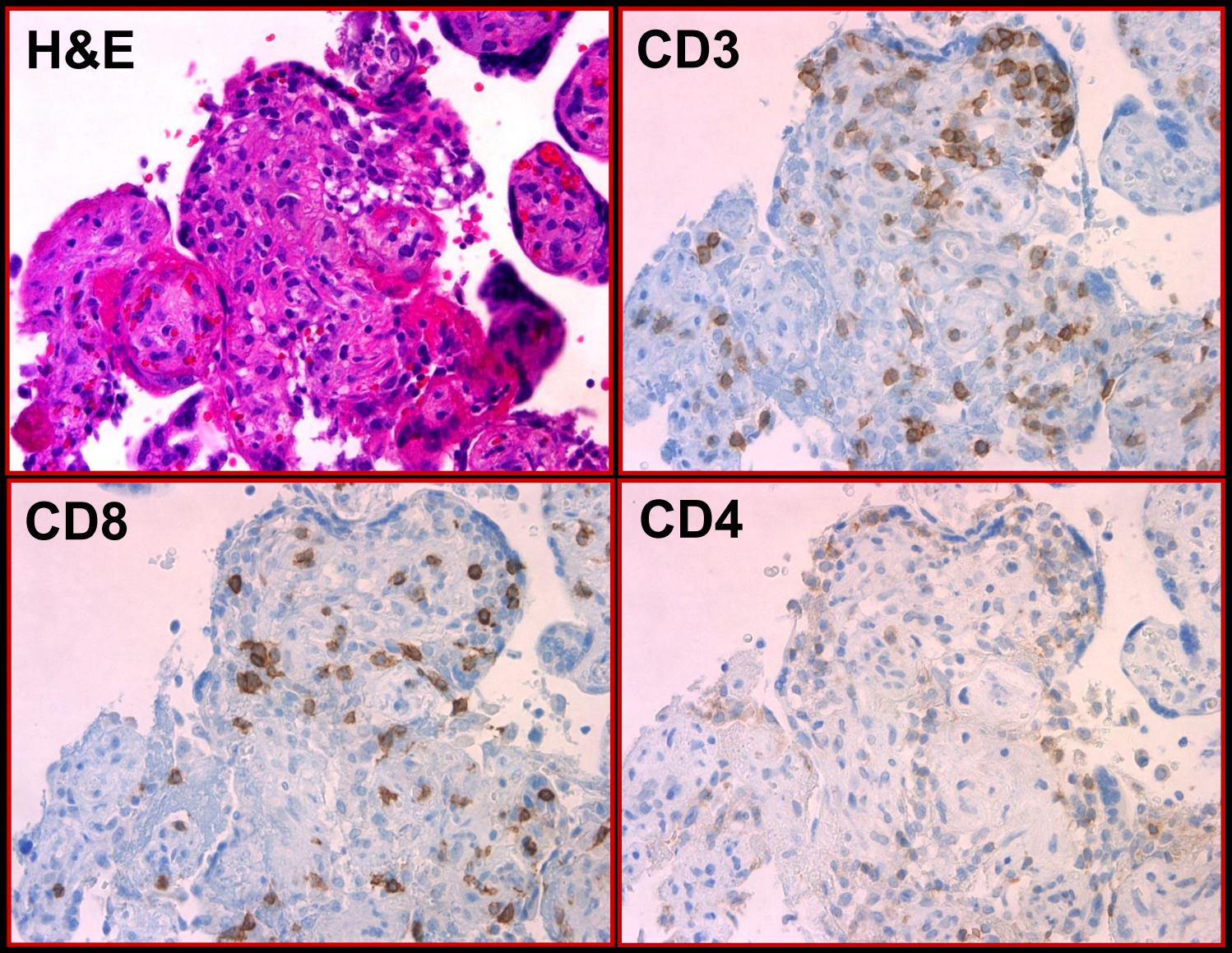
Chronic Placentitis (villitis)

- **Infectious**
- ***Idiopathic*** ***(Villitis of Unknown Etiology; VUE)***
  - **5-15% all term placentas**
  - **semi-allograft rejection**
  - ***maternal T cell infiltration***
  - **CD8+ T cell predominant**
  - **fetal growth restriction, fetal death**

Chorionic Villi

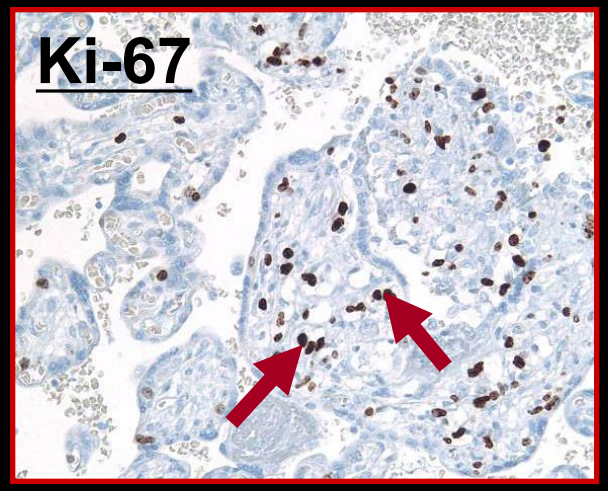


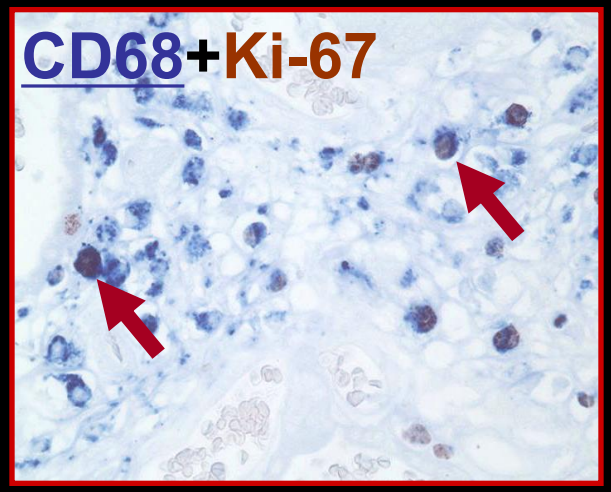
Villitis of Unknown Etiology

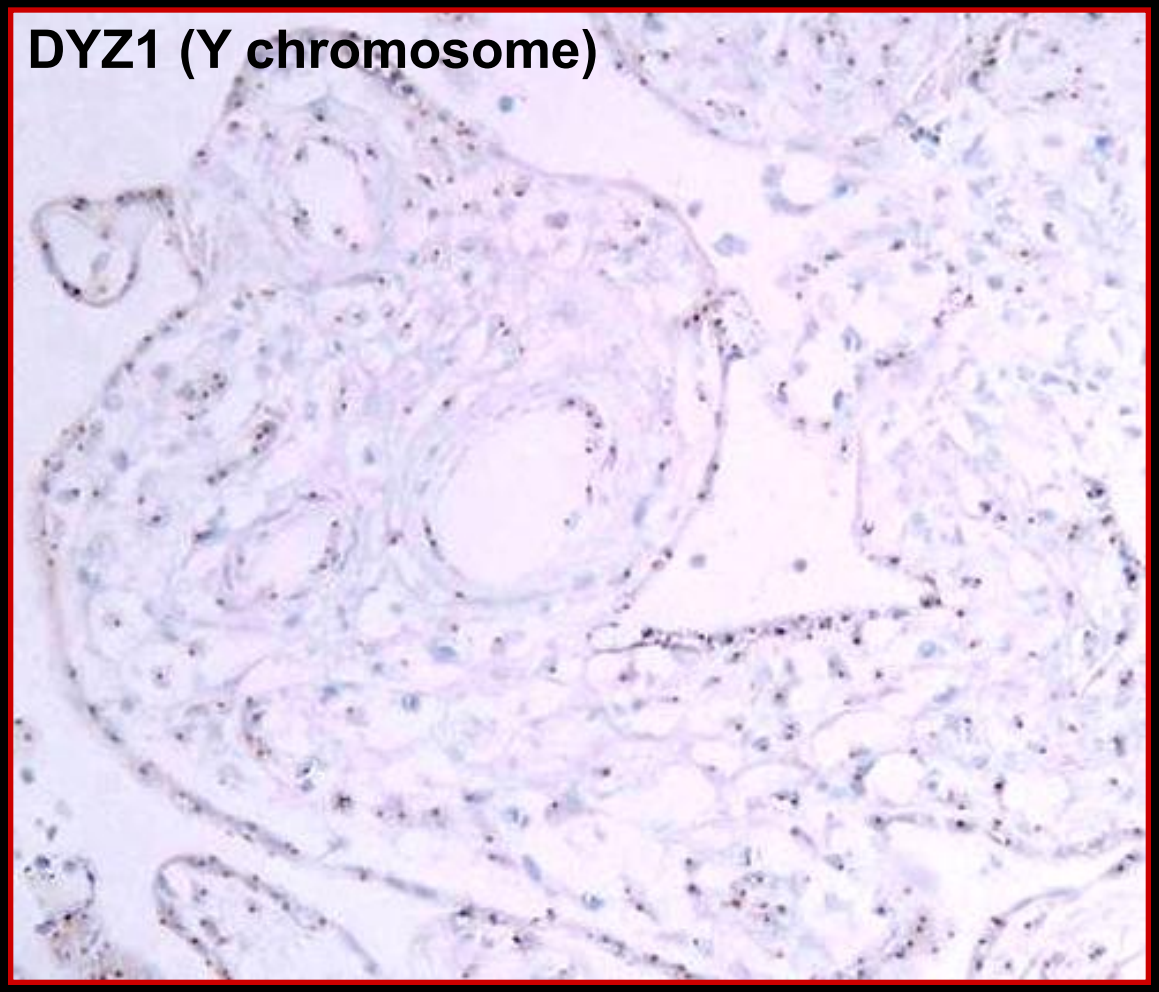


Kim JS et al. Histopathology 2008;52:457

Villitis of Unknown Etiology: Involvement of Fetal Macrophages



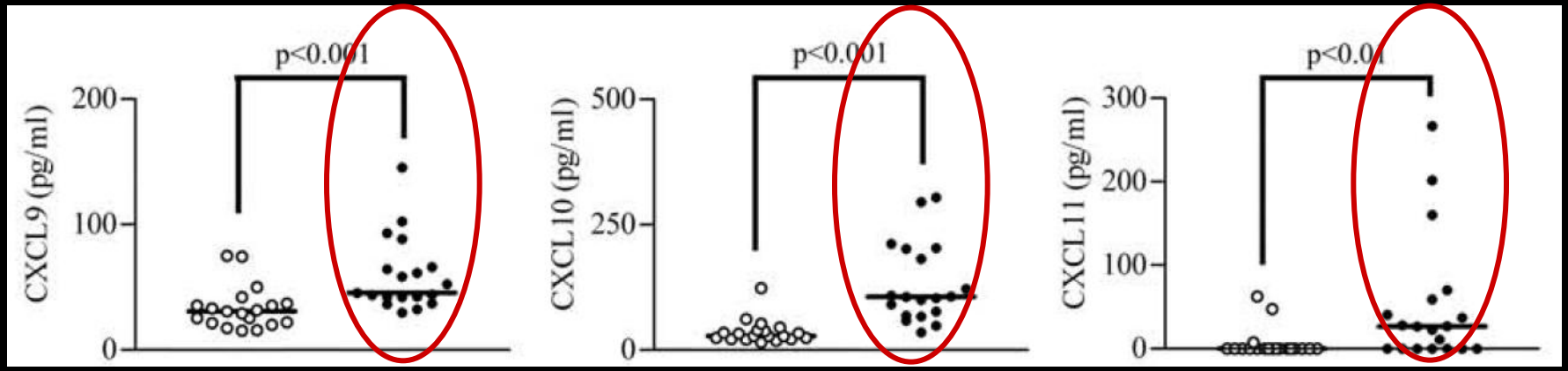




Chromogenic *in situ* hybridization (CISH)

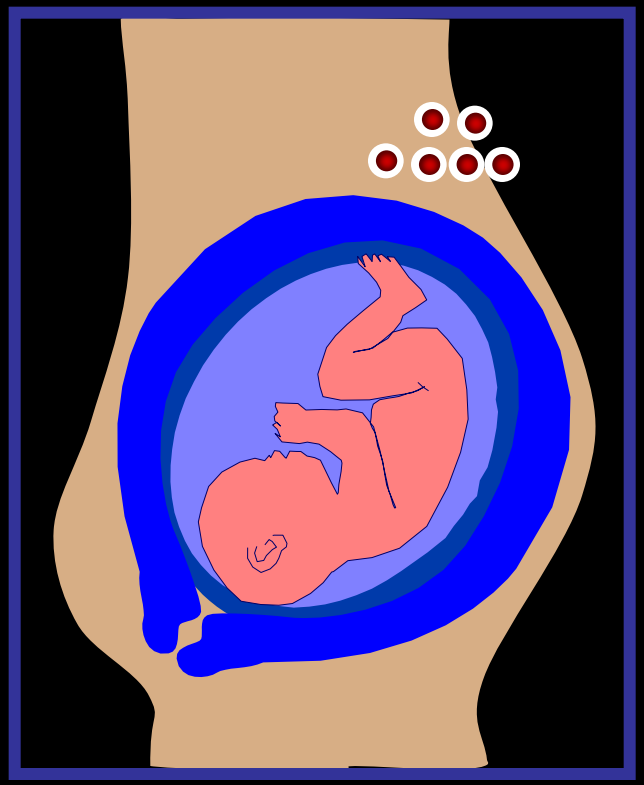
Kim JS et al. Histopathology 2008;52:457

Fetal Plasma T-Cell Chemokine Concentrations: Villitis of Unknown Etiology (VUE)



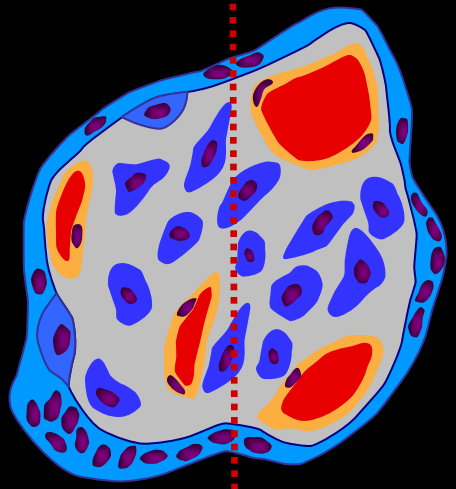
Kim MJ et al. J Immunol 2009;182:3919

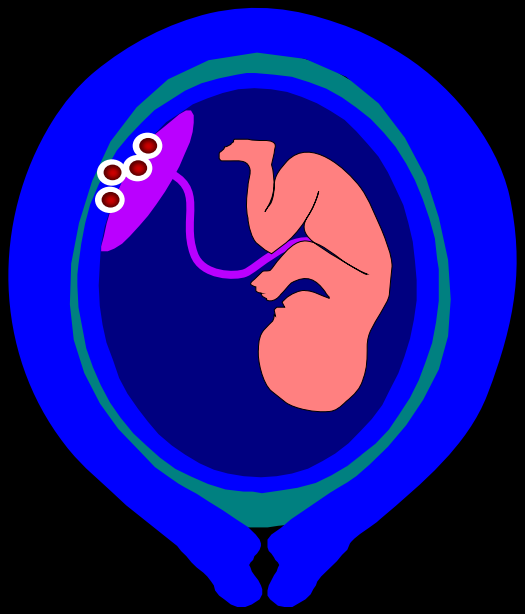
Villitis of Unknown Etiology Is Associated with a Distinct Pattern of Chemokine Up-Regulation in the Feto-Maternal and Placental Compartments: Implications for Conjoint Maternal Allograft Rejection and Maternal Anti-Fetal Graft-versus-Host Disease[1]



Allograft rejection

Graft vs. Host Disease (GVHD) = Fetus





● : maternal T cells

● : placental macrophages (Hofbauer cells)

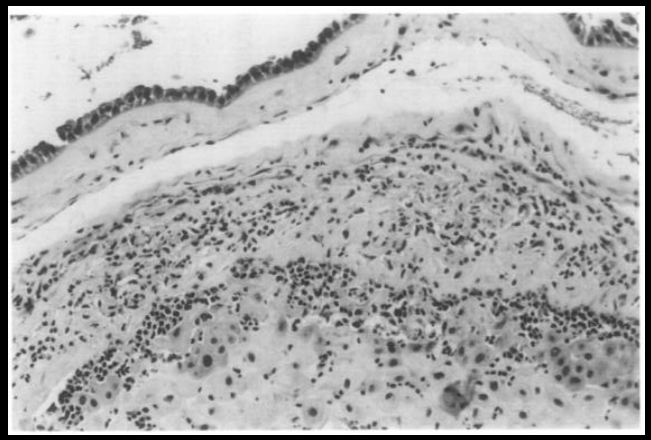
Kim MJ et al. J Immunol 2009;182:3919

Chronic Chorioamnionitis vs. VUE

1. Gersell DJ et al. Chronic chorioamnionitis: A clinicopathologic study of 17 cases. Int J Gynecol Pathol 1991;10:217-29

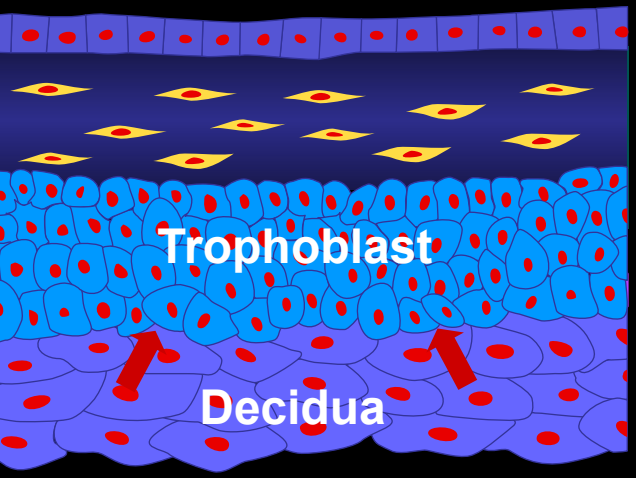
2. Jacques SM, Qureshi F. Chronic chorioamnionitis: A clinicopathologic and immunohistochemical study. Hum Pathol 1998;29:1457-61

Study 1 and 2 combined (n=48):
Preterm birth: 52%
VUE (+): 69%

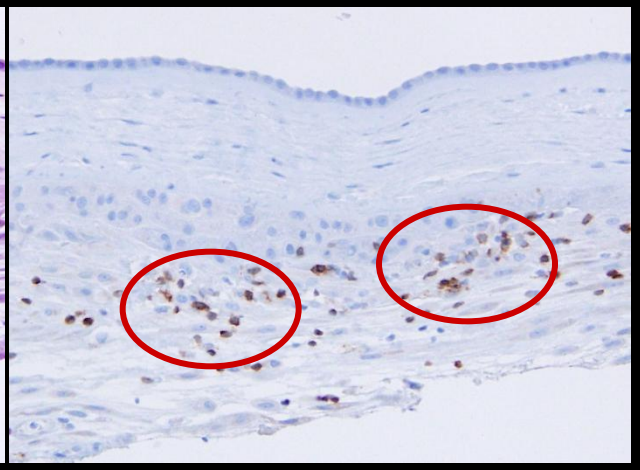


Histologic Diagnostic Criteria:
Amniotropic infiltration of maternal T cells into the chorioamniotic membranes

Modified Diagnostic Criteria: Chronic Chorioamnionitis



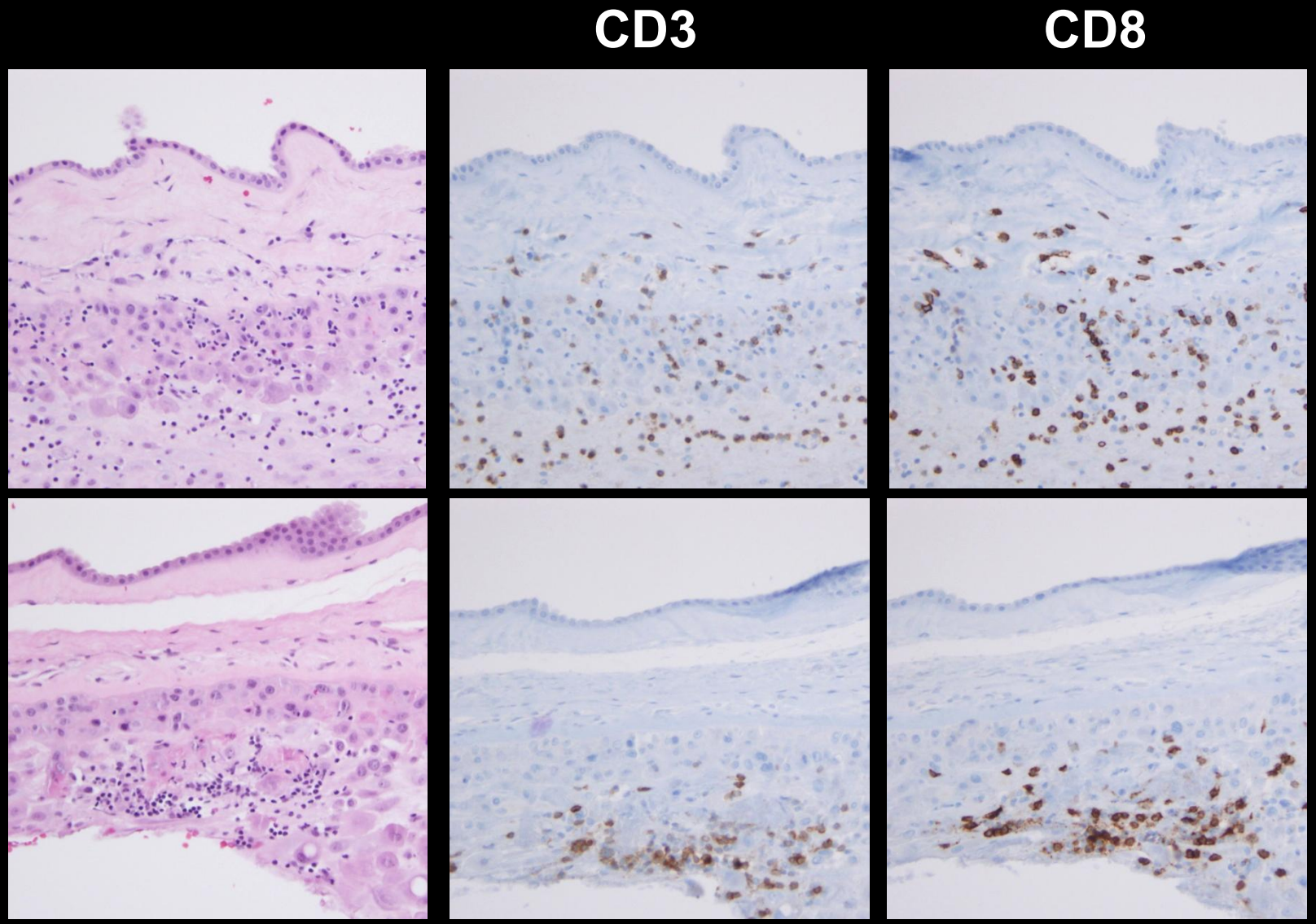
H&E



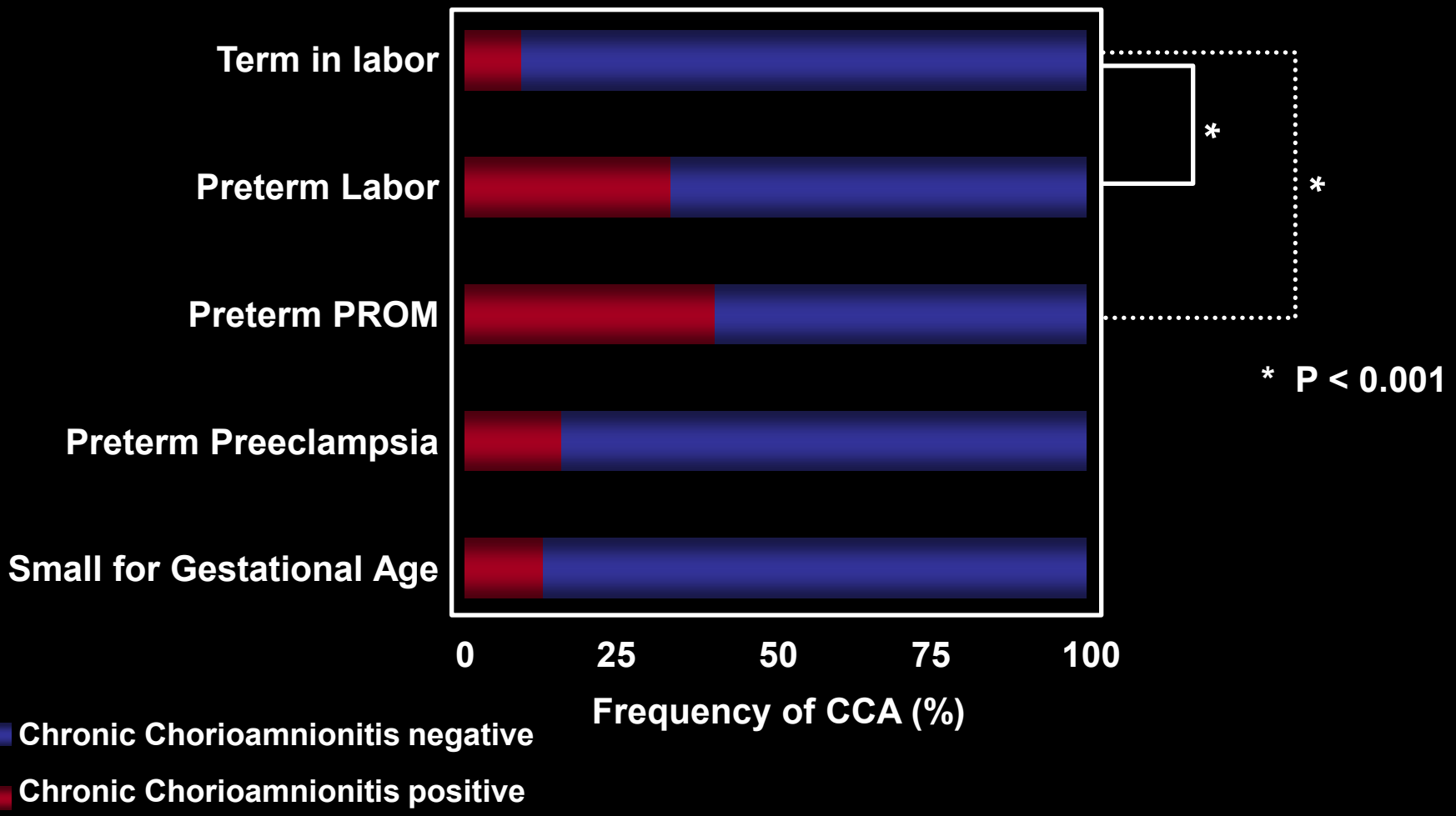
CD3+ T cells

Kim CJ et al. Mod Pathol 2010;23:1000-11

Chronic Chorioamnionitis



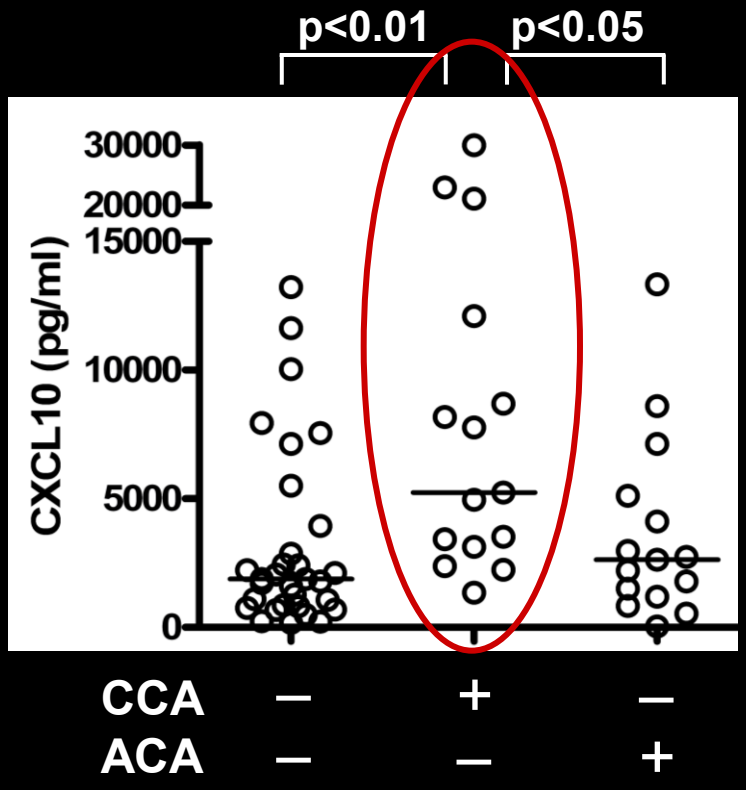
Frequency of Chronic Chorioamnionitis In Different Obstetrical Settings



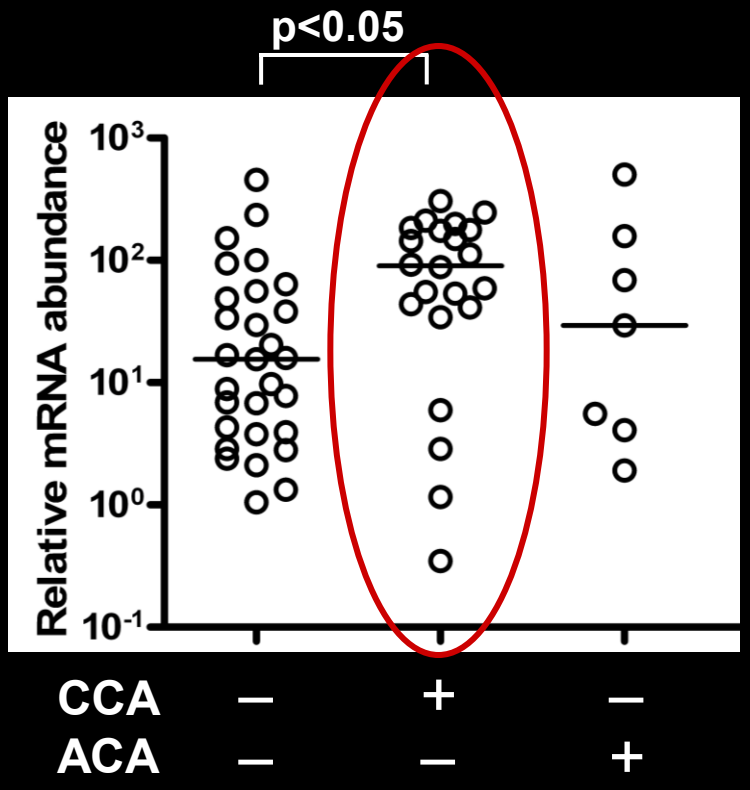
Kim CJ et al. Mod Pathol 2010;23:1000-11

CXCL10 in Amniotic Fluid and the Chorioamniotic Membranes

Amniotic Fluid



Chorioamniotic Membranes



CCA: Chronic chorioamnionitis
ACA: Acute chorioamnionitis

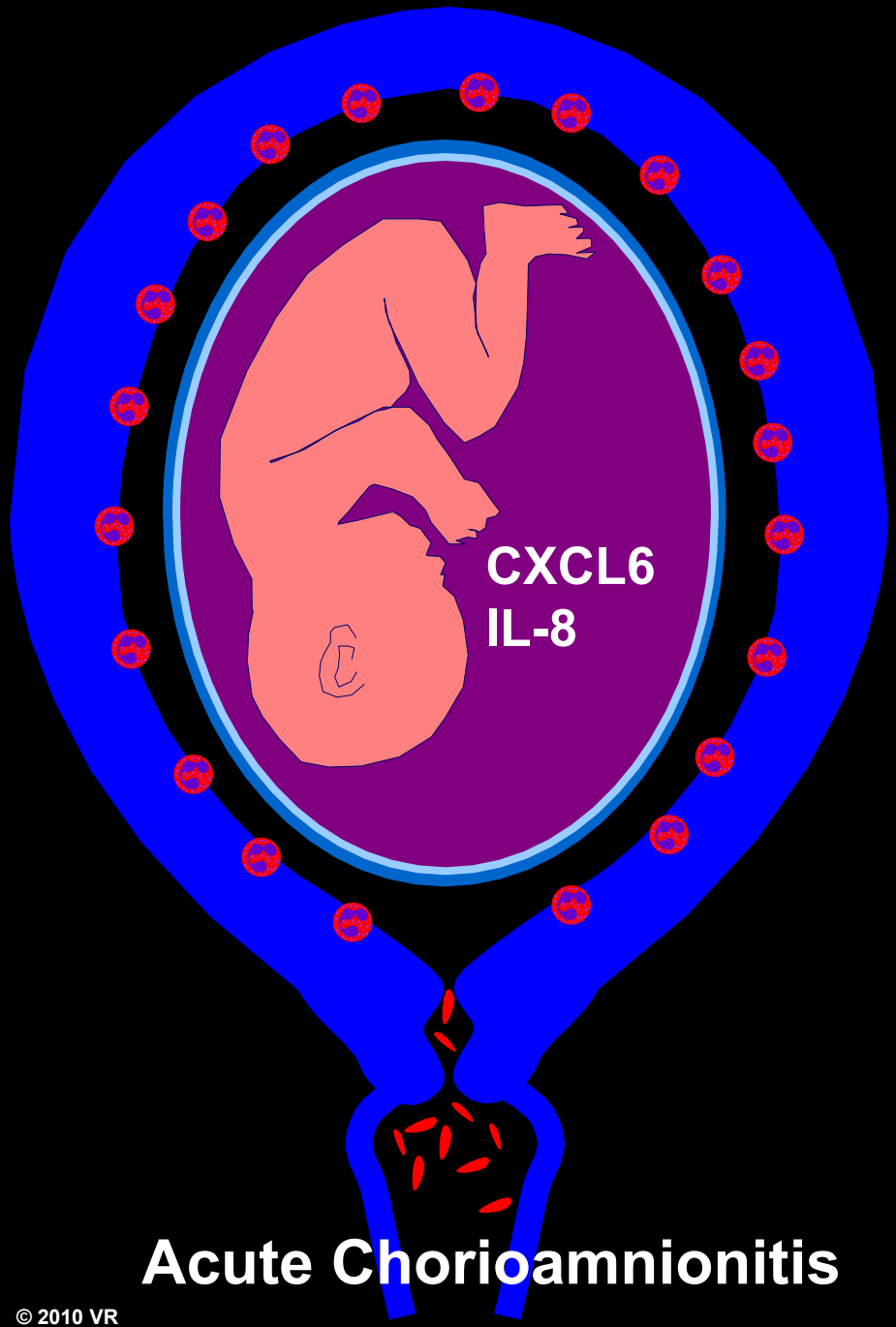
Kim CJ et al. Mod Pathol 2010;23:1000-11

- **Villitis of Unknown Etiology:**
  - **Maternal Anti-fetal Rejection:**
    Villous type
- **Chronic Chorioamnionitis:**
  - **Maternal Anti-fetal Rejection:**
    Membranous type

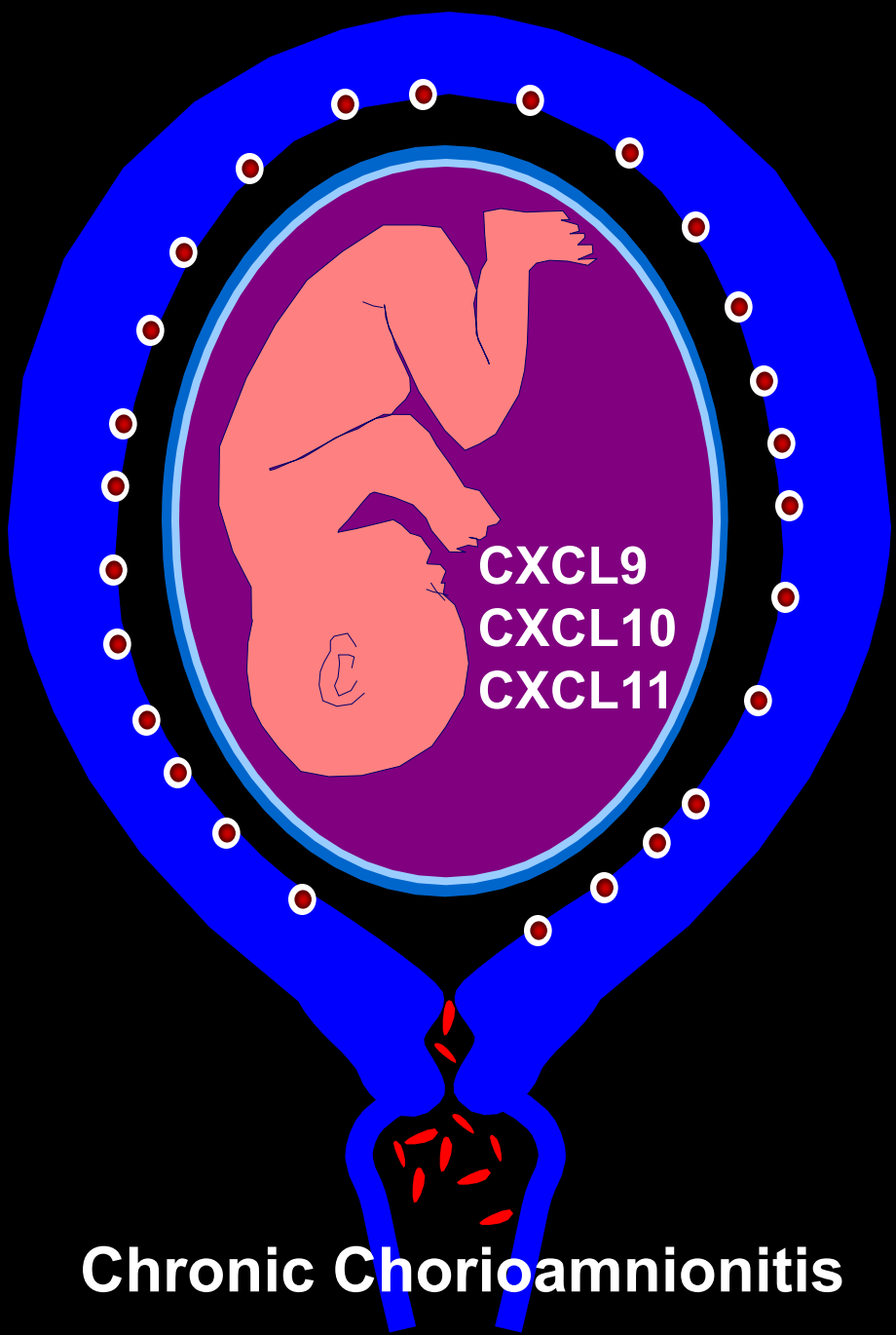
Summary

- Acute and chronic placental inflammatory lesions are the most common pathologies of preterm birth

- Acute chorioamnionitis and funisitis are responses to intra-amniotic infection and inflammation, while chronic chorioamnionitis and villitis are manifestations of maternal anti-fetal rejection



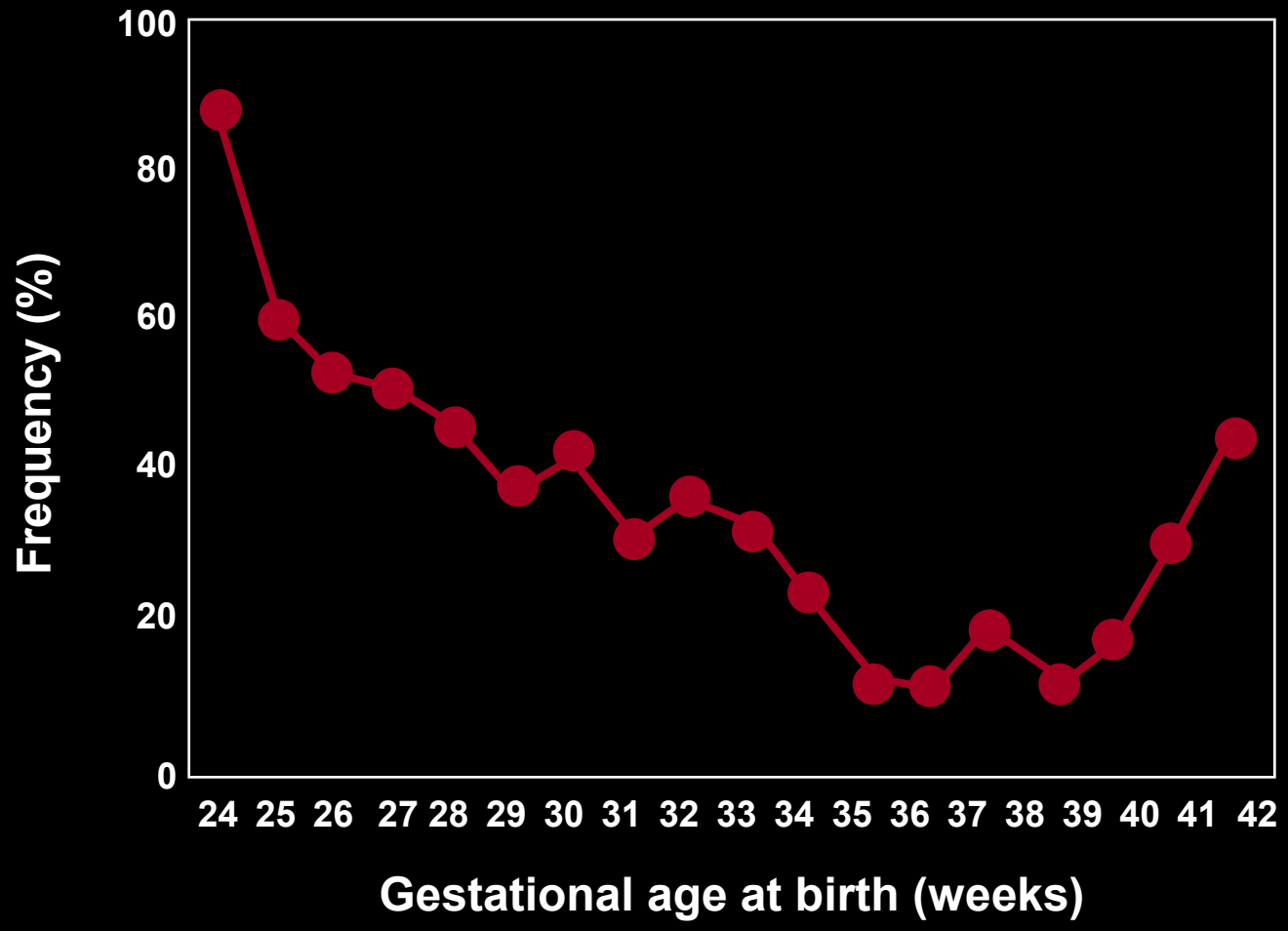
Acute Chorioamnionitis



Chronic Chorioamnionitis

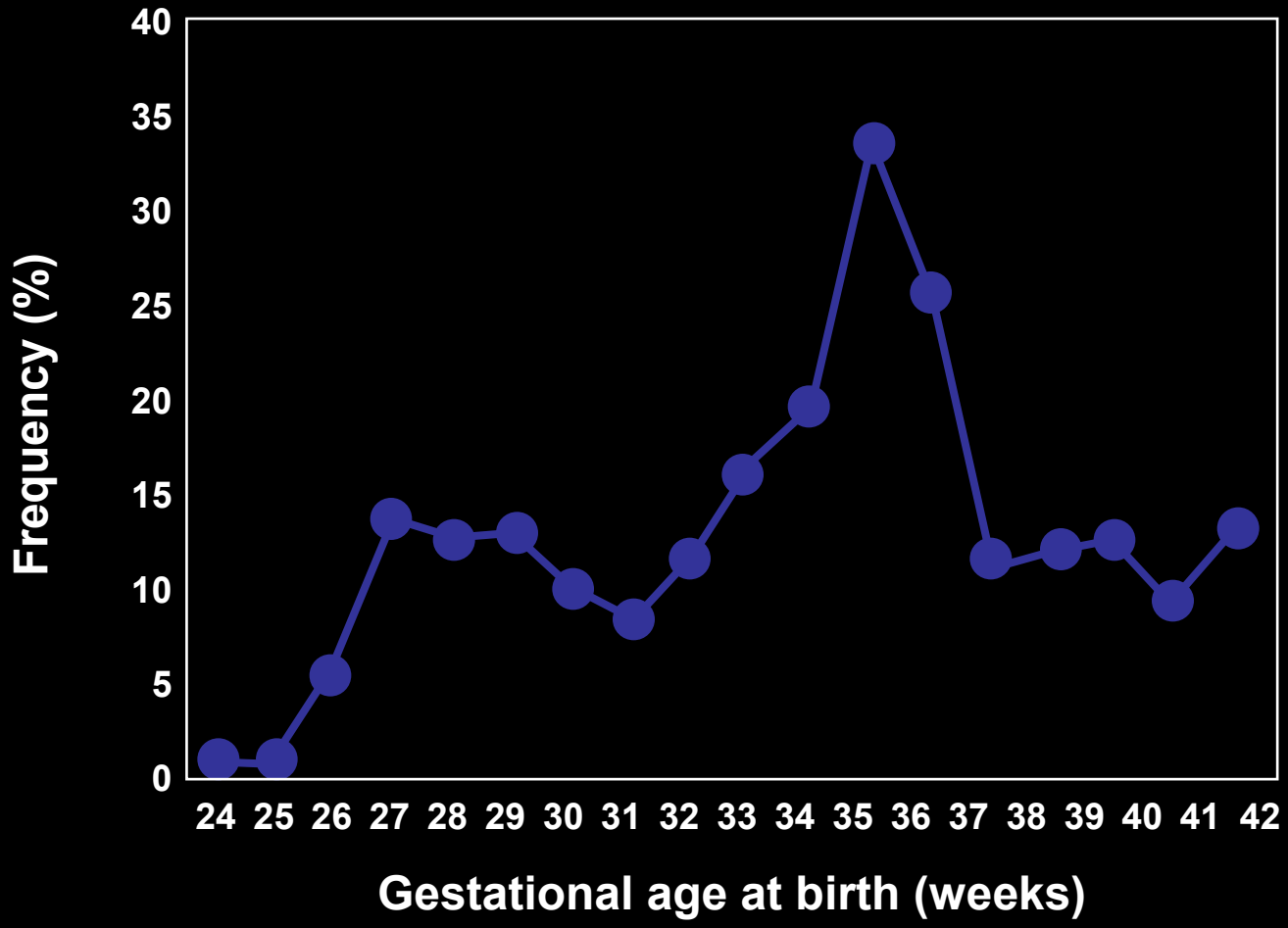
What is the Frequency of Placental Lesions as a Function of Gestational Age at Birth?

Acute Chorioamnionitis: A Consecutive Preterm Birth Cohort (n = 1,492)



Lee J et al. Placenta 2013:34:681

Chronic Chorioamnionitis: A Consecutive Preterm Birth Cohort (n = 1,492)



Lee J et al. Placenta 2013:34:681

Acute Chorioamnionitis is the Most Common Lesion in Extremely Preterm Birth

Chronic Chorioamnionitis is the Most Common Lesion in Late Preterm Birth

Lee J et al. Placenta 2013:34:681

Allograft Rejection

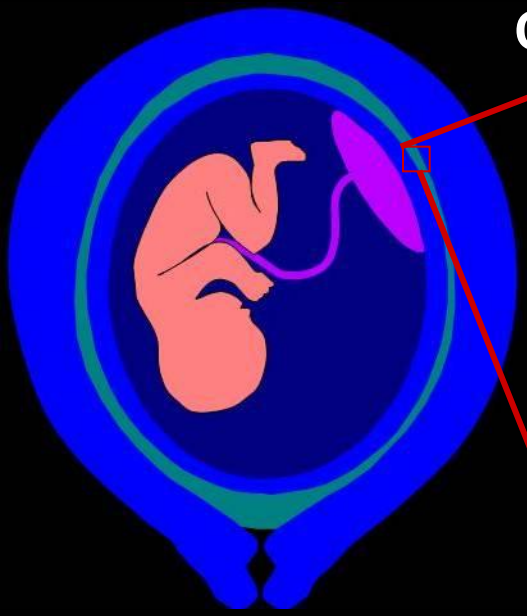
- Cellular Rejection
- Humoral Antibody-Mediated Rejection

Risk Factors of HLA Sensitization and Allograft Rejection

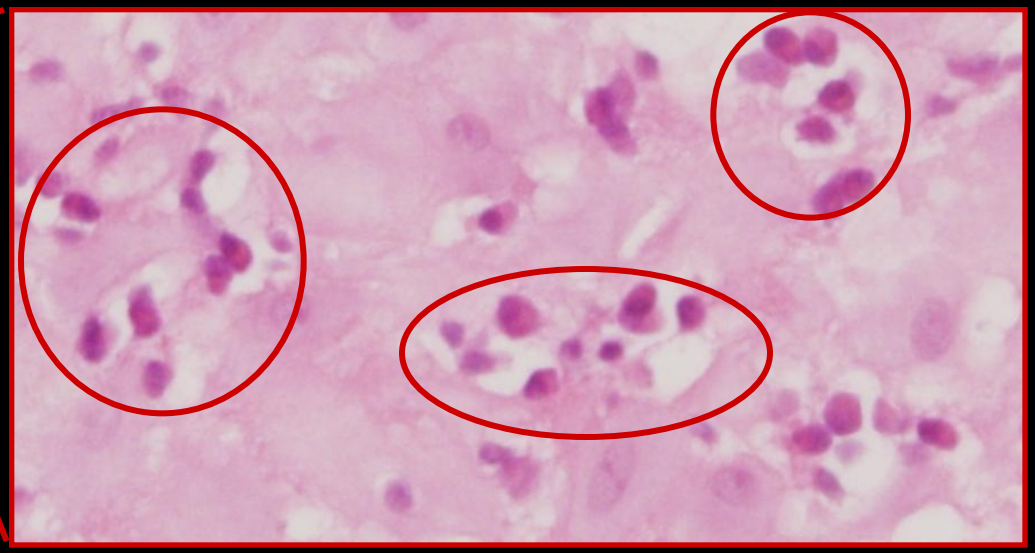
- Pregnancy
- Organ transplantation
- Blood transfusion

Sanfilippo F et al. Transplantation 1982;34:360
Scornik JC et al. Transplantation 1997;37:249
Rebibou JM et al. Transplantation 2002;74:537

Antibody-Mediated Rejection

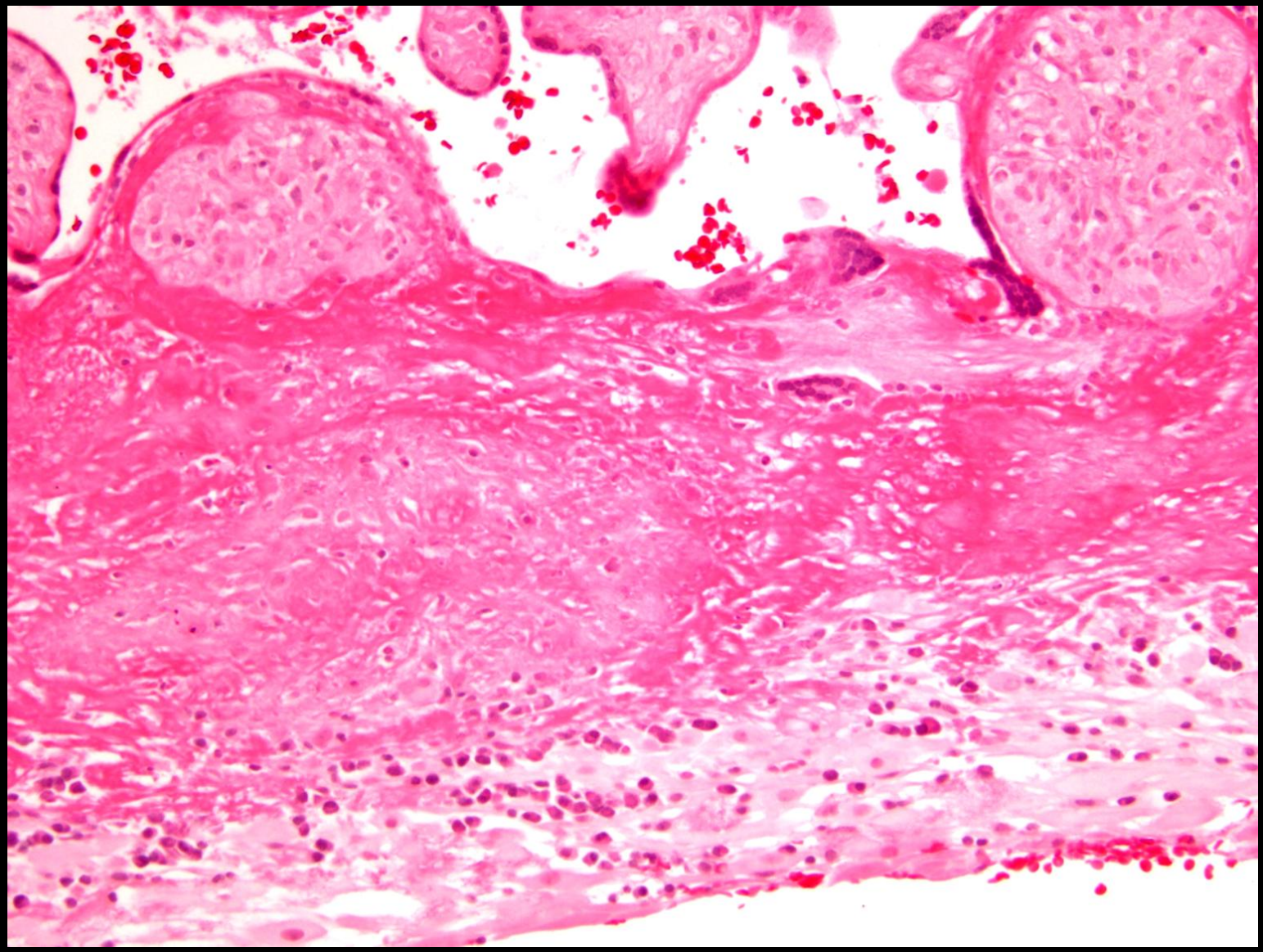


Chronic deciduitis with plasma cells (maternal)



Antibodies against
Donor (fetus)-specific Antigen:
- **Anti-HLA class I**
- **Anti-HLA class II**

Chronic Deciduitis with Plasma Cells



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PLoS one

A Signature of Maternal Anti-Fetal Rejection in Spontaneous Preterm Birth: Chronic Chorioamnionitis, Anti-Human Leukocyte Antigen Antibodies, and C4d

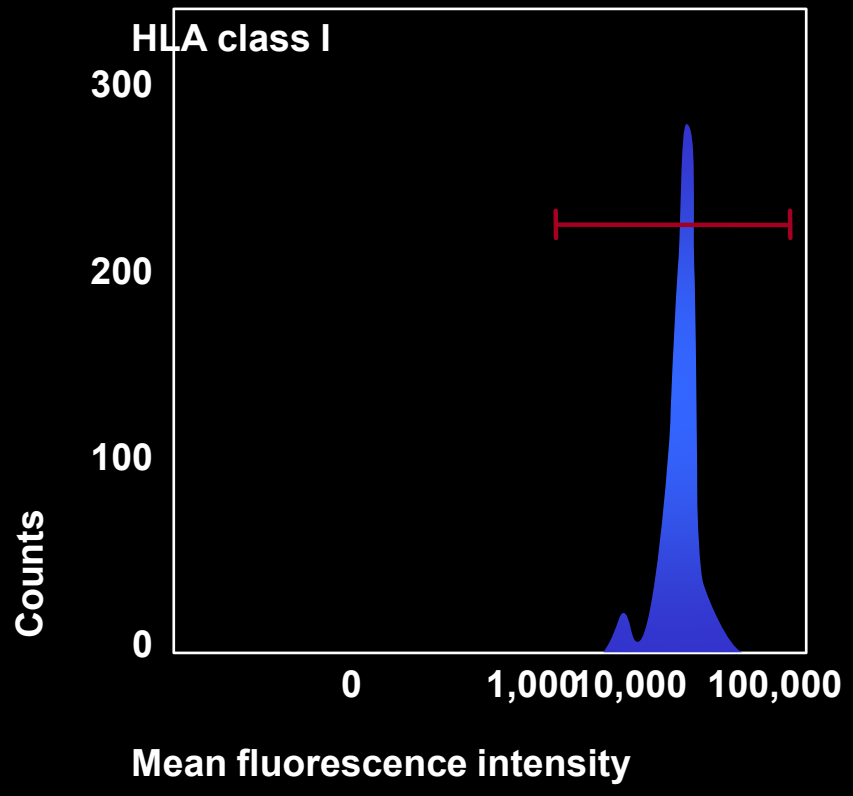
JoonHo Lee[1], Roberto Romero[1,2,3]*, Yi Xu[1], Jung-Sun Kim[4], Vanessa Topping[1], Wonsuk Yoo[5], Juan Pedro Kusanovic[1,6,7], Tinnakorn Chaiworapongsa[1,2], Sonia S. Hassan[1,2], Bo Hyun Yoon[8], Chong Jai Kim[1,9]*

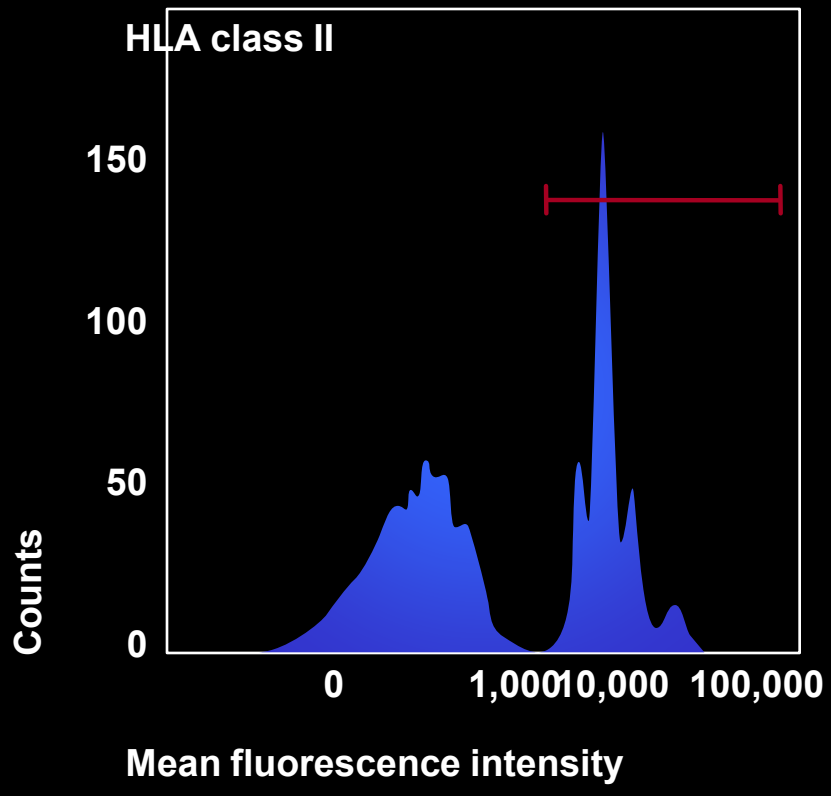
Methods

- **Cross-sectional study:**
  - **Term birth (n=140):**
    - **term not in labor (n=70)**
    - **term in labor (n=70)**
  - **Spontaneous preterm birth (n=140):**
    - **preterm labor with intact membranes (n=70)**
    - **preterm prelabor rupture of membranes (n=70)**
- **Flow cytometry:**
  - **maternal and fetal sera for HLA class I and class II panel-reactive antibodies (PRA)**

Lee et al. PLoS ONE 2011:6:e16806

Flow Cytometry:
FlowPRA®-I and –II Screening Tests





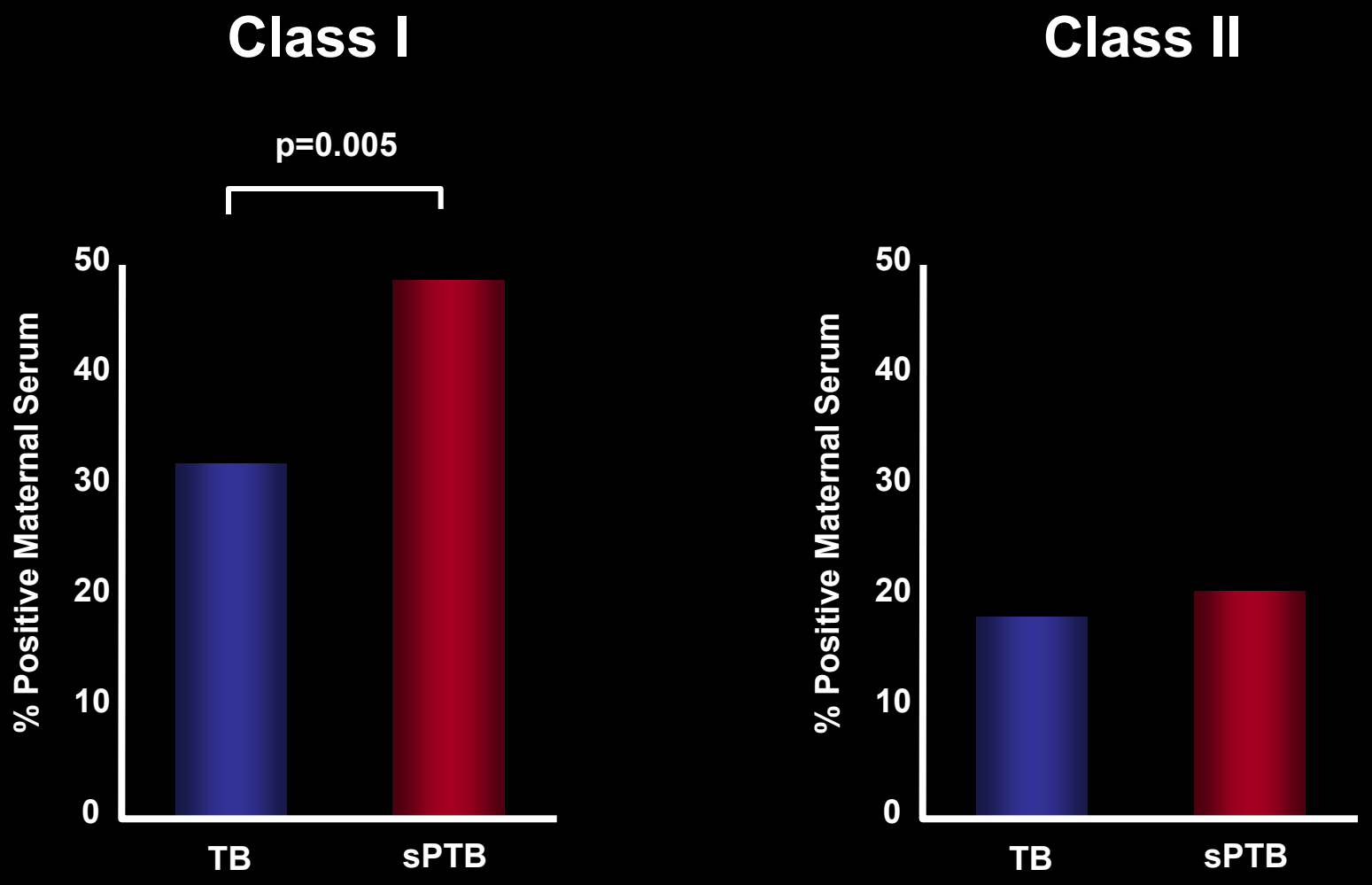
Maternal serum:

Anti-HLA class I Ab (+)

Anti-HLA class II Ab (+)

Lee et al. PLoS ONE 2011:6:e16806

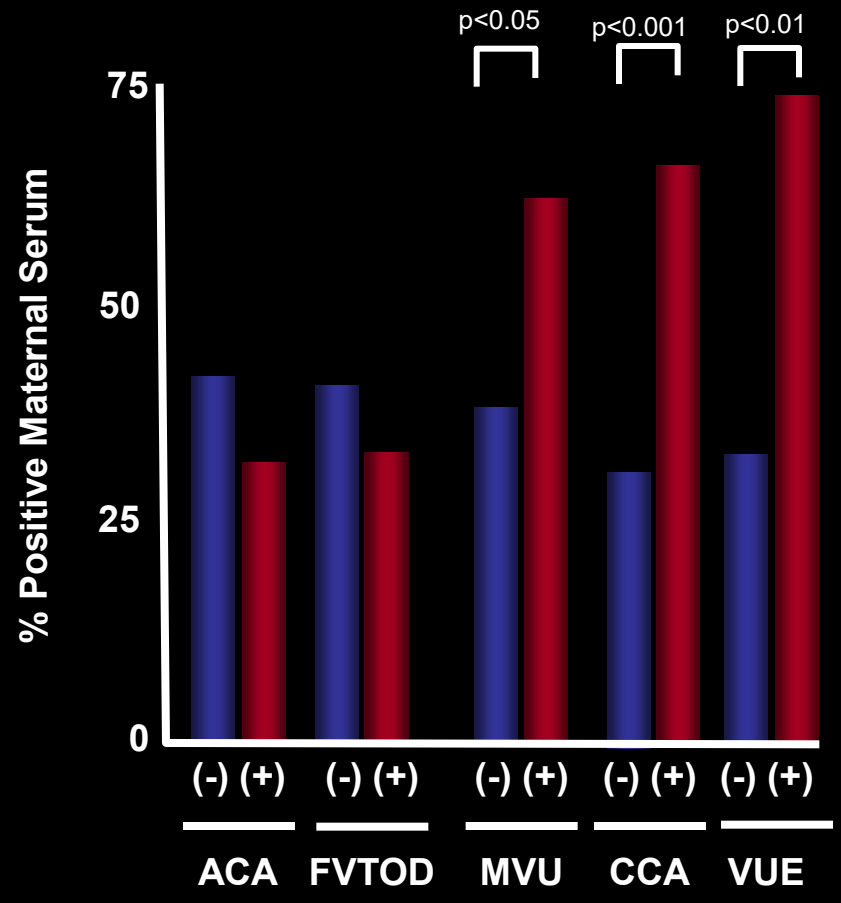
IgG HLA PRA Positivity in Maternal Serum at the Time of Delivery

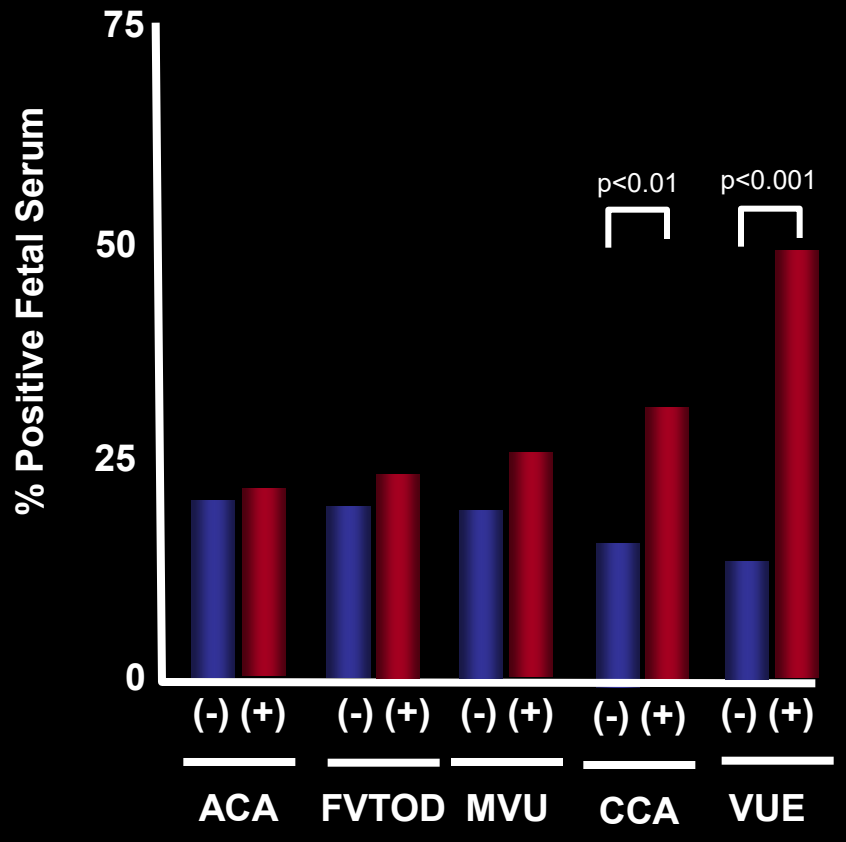


TB: Term birth
sPTB: Spontaneous preterm birth

Lee et al. PLoS ONE 2011:6:e16806

HLA Class I PRA positivity and Placental Pathology





CCA: Chronic chorioamnionitis
VUE: Villitis of unknown etiology
ACA: Acute chorioamnionitis
MVU: Maternal vascular underperfusion
FVTOD: Fetal vascular thrombo-occlusive disease

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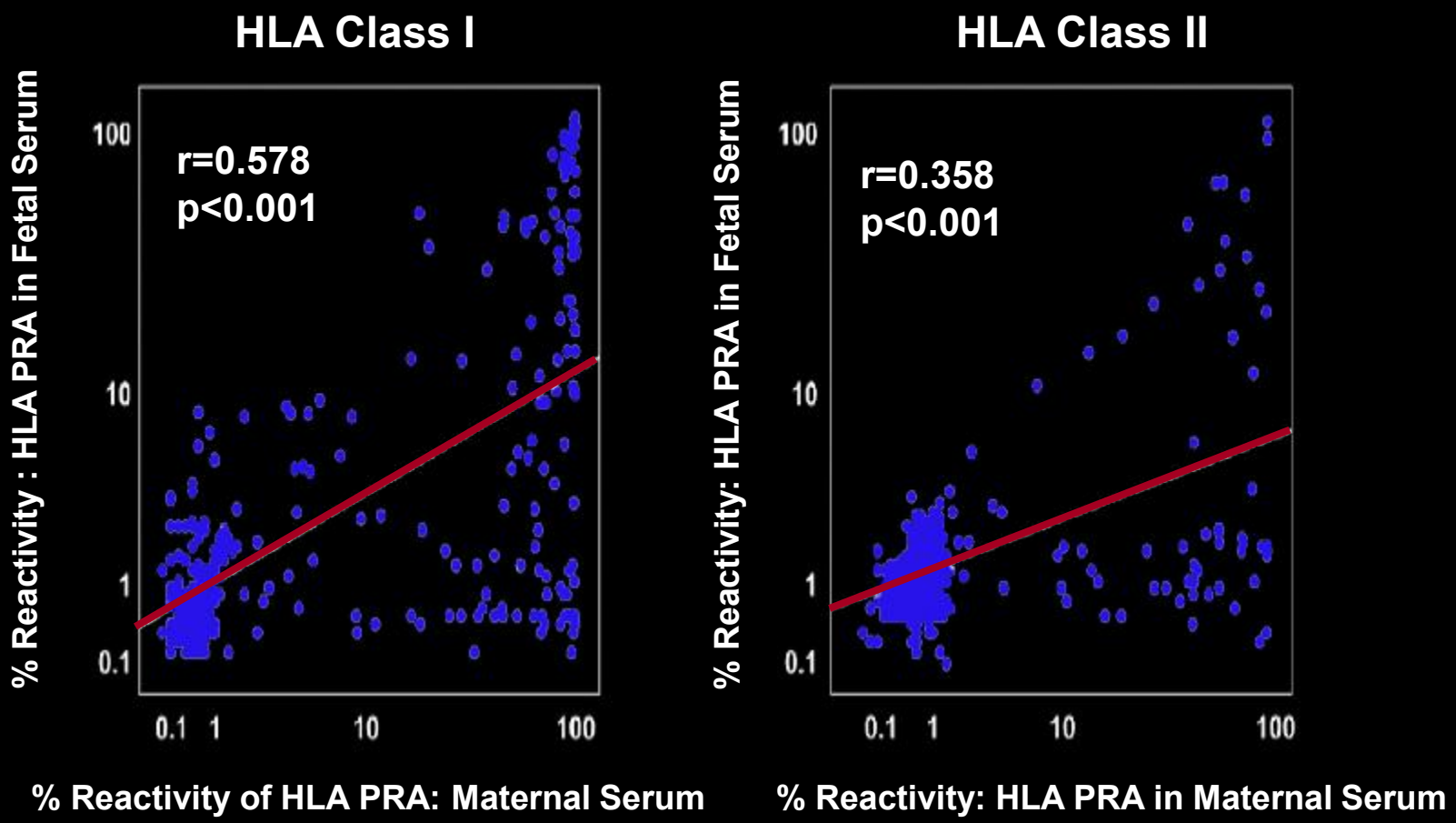
Correlation between Maternal and Fetal HLA PRA



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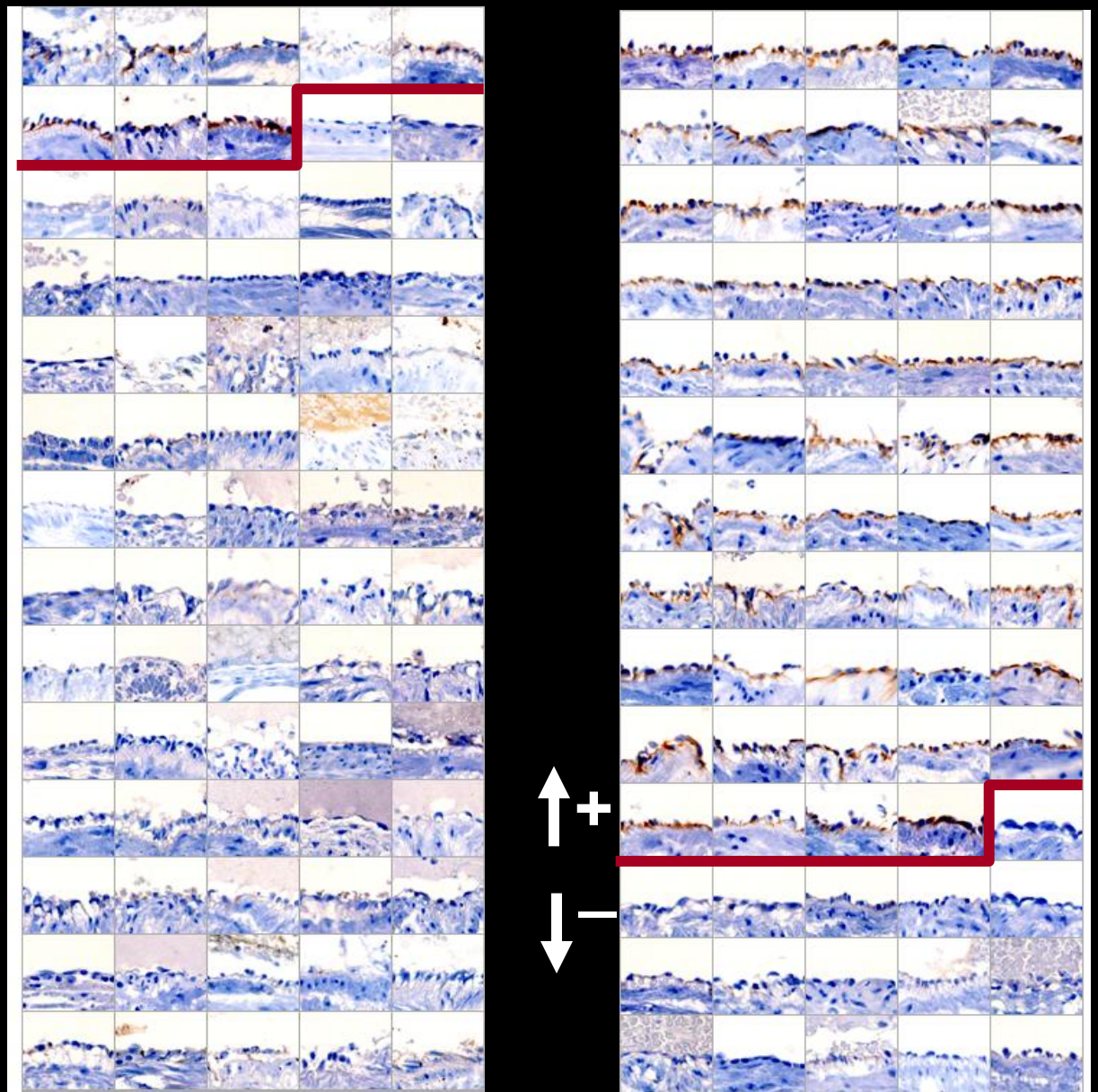
C4d Deposition on Umbilical Vein Endothelium

Term in Labor (11.4% - 8/70)

Preterm Labor/Delivery (77.1% - 54/70)



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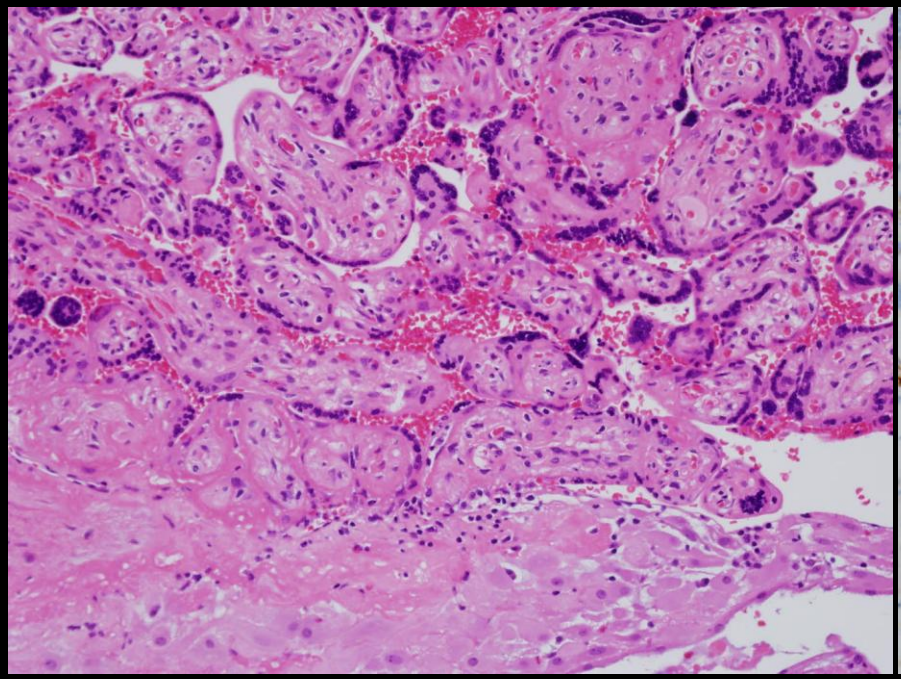
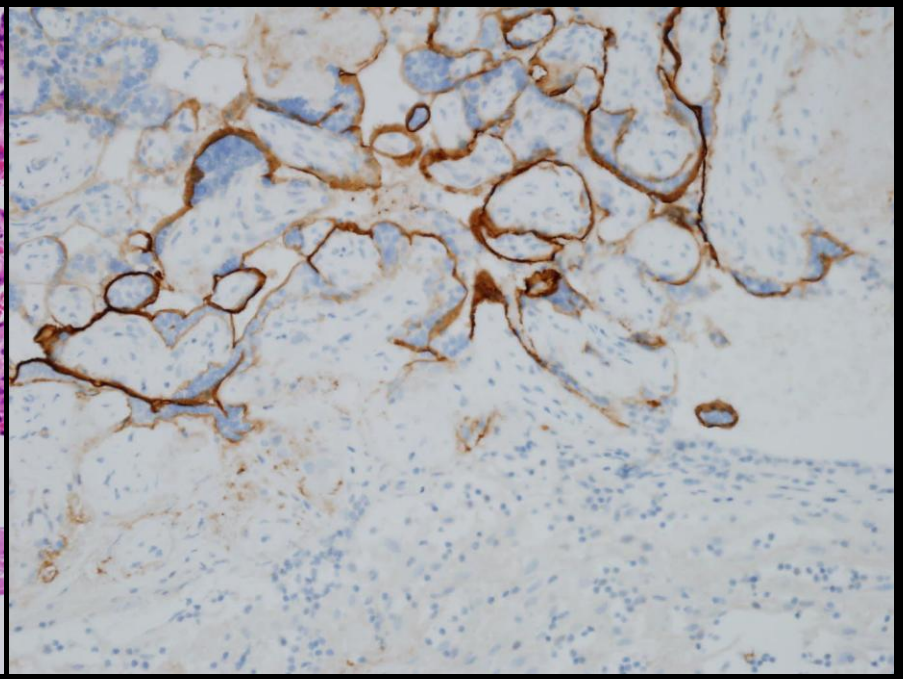
Lee et al. PLoS ONE 2011:6:e16806

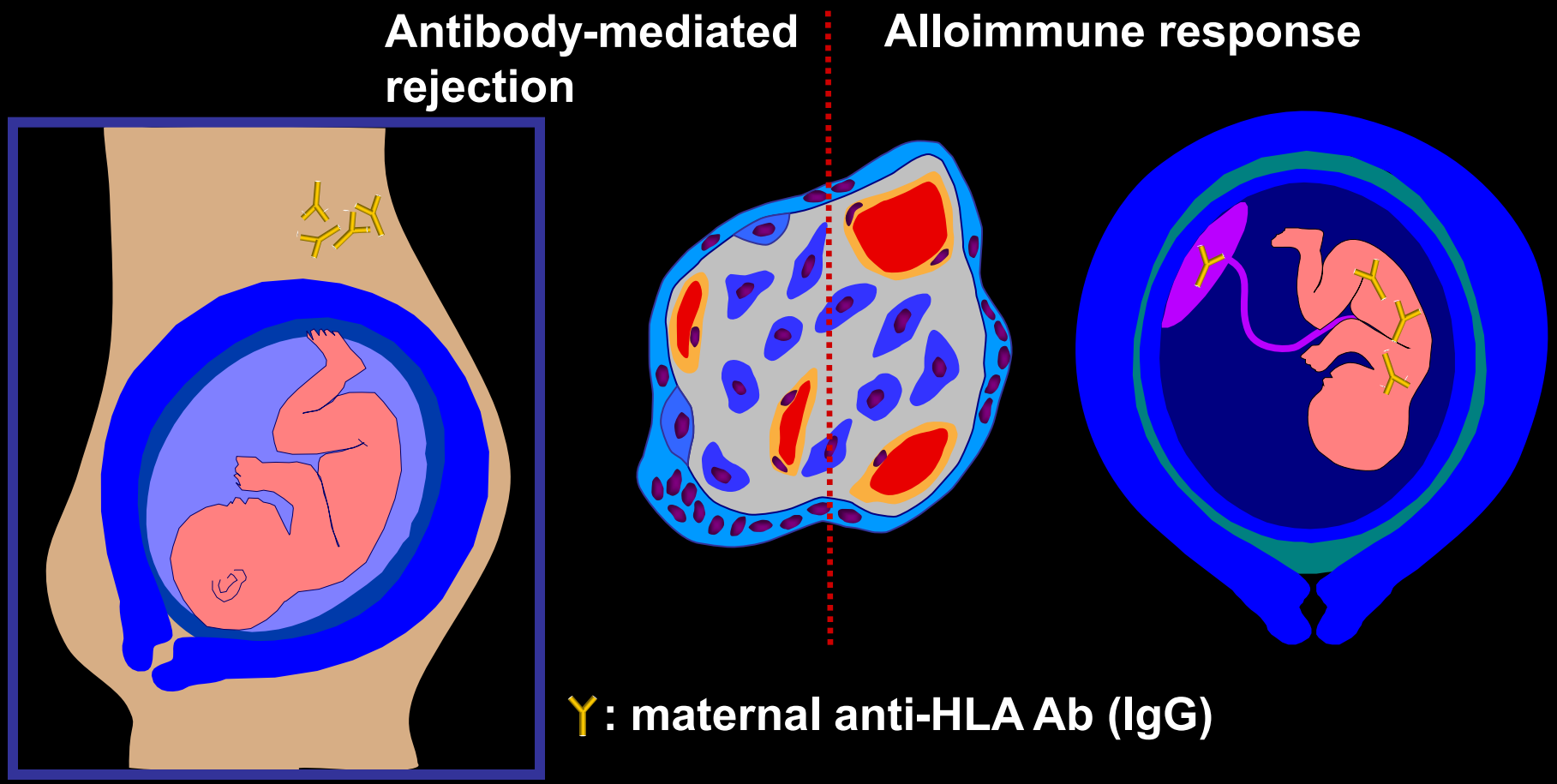
Villitis of Unknown Etiology: Placental C4d



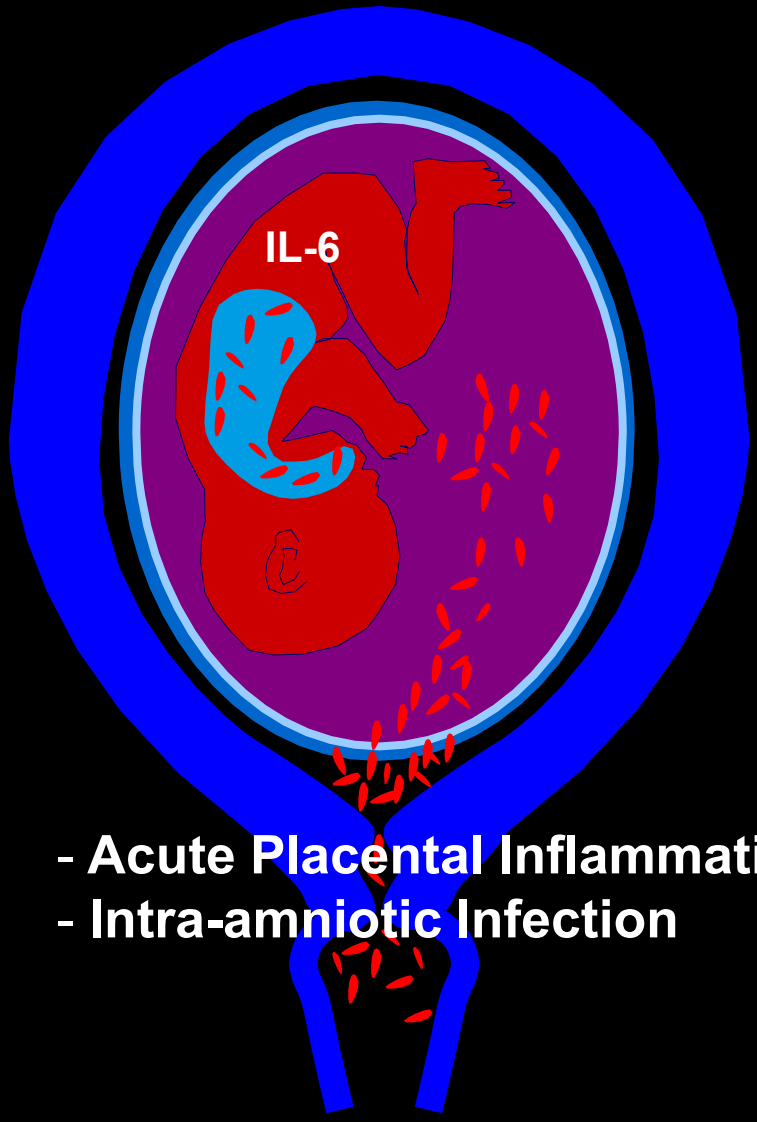


Lee KA et al. Placenta 2013;34:432

Maternal Anti-Fetal Antibody-Mediated Rejection

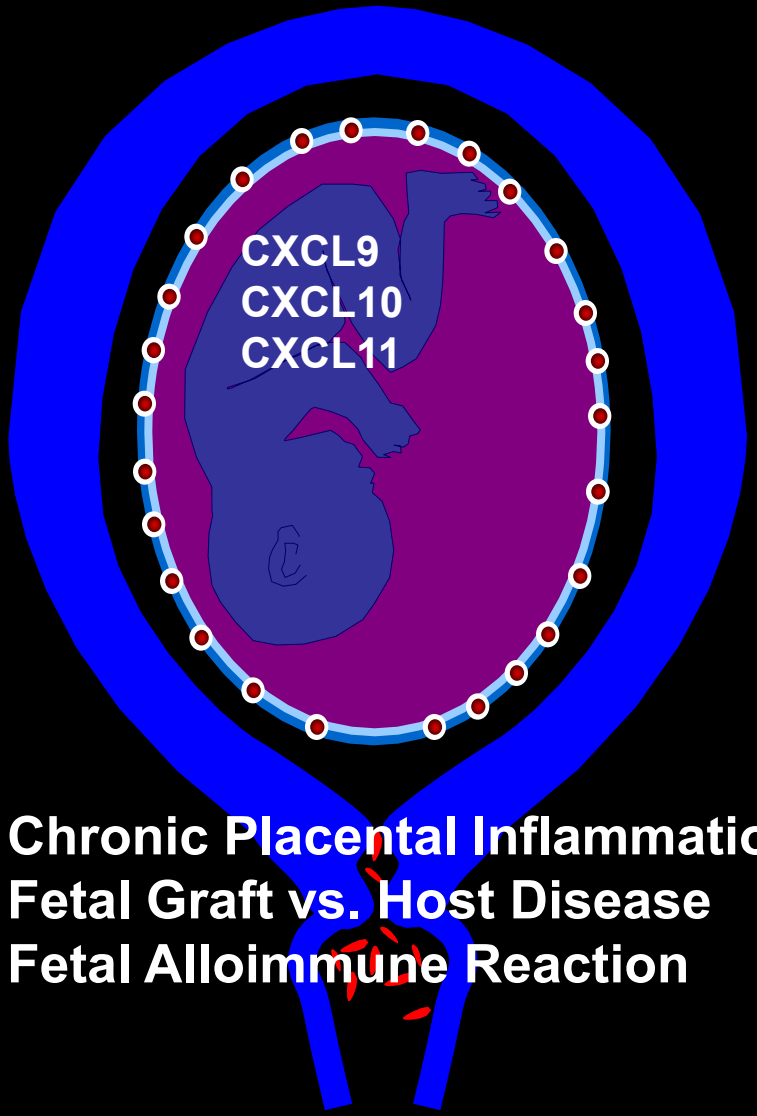


FIRS Type I

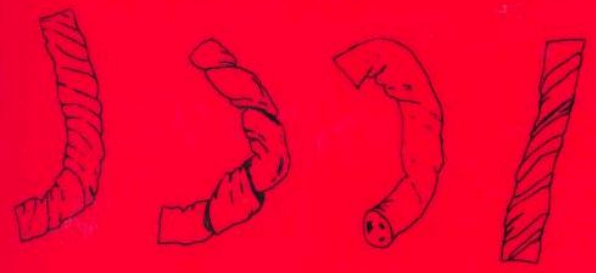


- Acute Placental Inflammation
- Intra-amniotic Infection

FIRS Type II



- Chronic Placental Inflammation
- Fetal Graft vs. Host Disease
- Fetal Alloimmune Reaction



The Placenta:
To Know Me Is To Love Me

A reference guide for gross placental examination

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