Female Reproductive Pathology: Failure of Pregnancy

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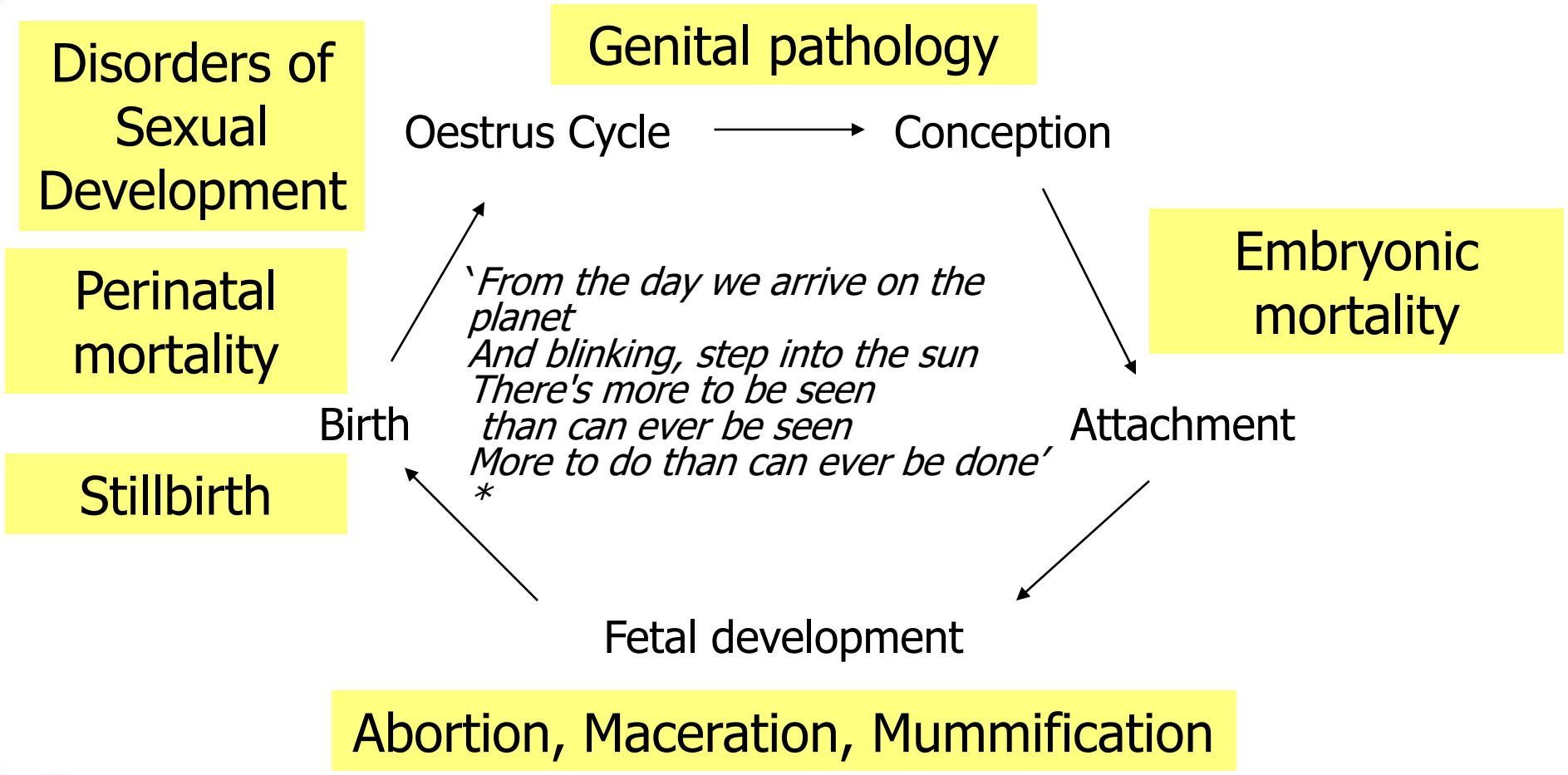
Circle of Reproductive Life*



* "Circle of Life" Music by Elton John, lyrics by Tim Rice, Performed by Elton John

Principles of Reproductive Pathology

- Know normal anatomy and histology
  - Use species, breed and age matched controls
- Always correlate Macroscopic (Gross) Pathology with Histology
- Know what to expect!
- What happens in one species will happen in another

Placenta in human/primate speak

- 'A flat cake' = disc = exchange area
- 'Membranes' = transparent membranes

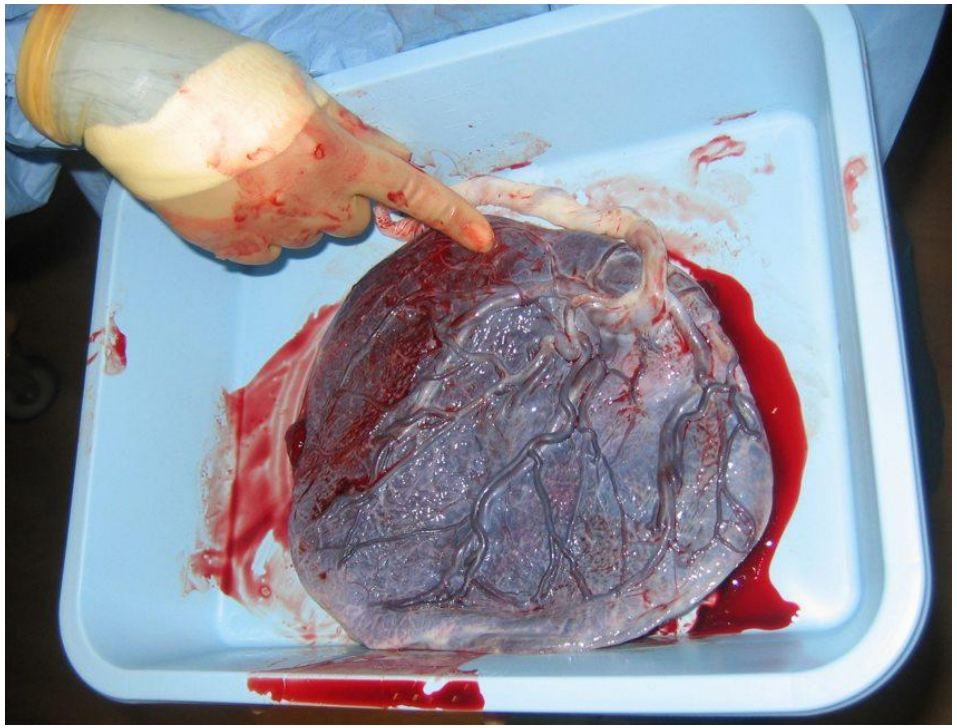


Photo complements of common.wikimedia.org

Reproduction

Reproduction occurs at the interface between aquatic and terrestrial environments.

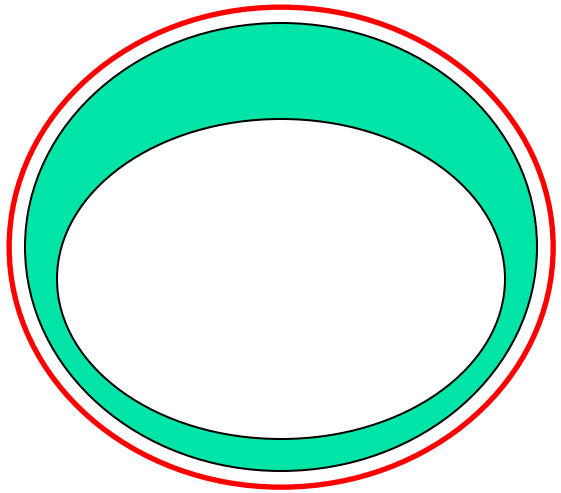
Far Beach, Mackay, Qld Australia

Mammals

- Amniotes (membrane around the fetus) – tetrapod vertebrates including amphibians, reptiles, mammals
- Mammals
  - Prototheria – Monotremes
  - Theria
    - Metatheria – Marsupials
    - Eutheria – placental mammals

Basic embryology

Zygote = fertilised ovum



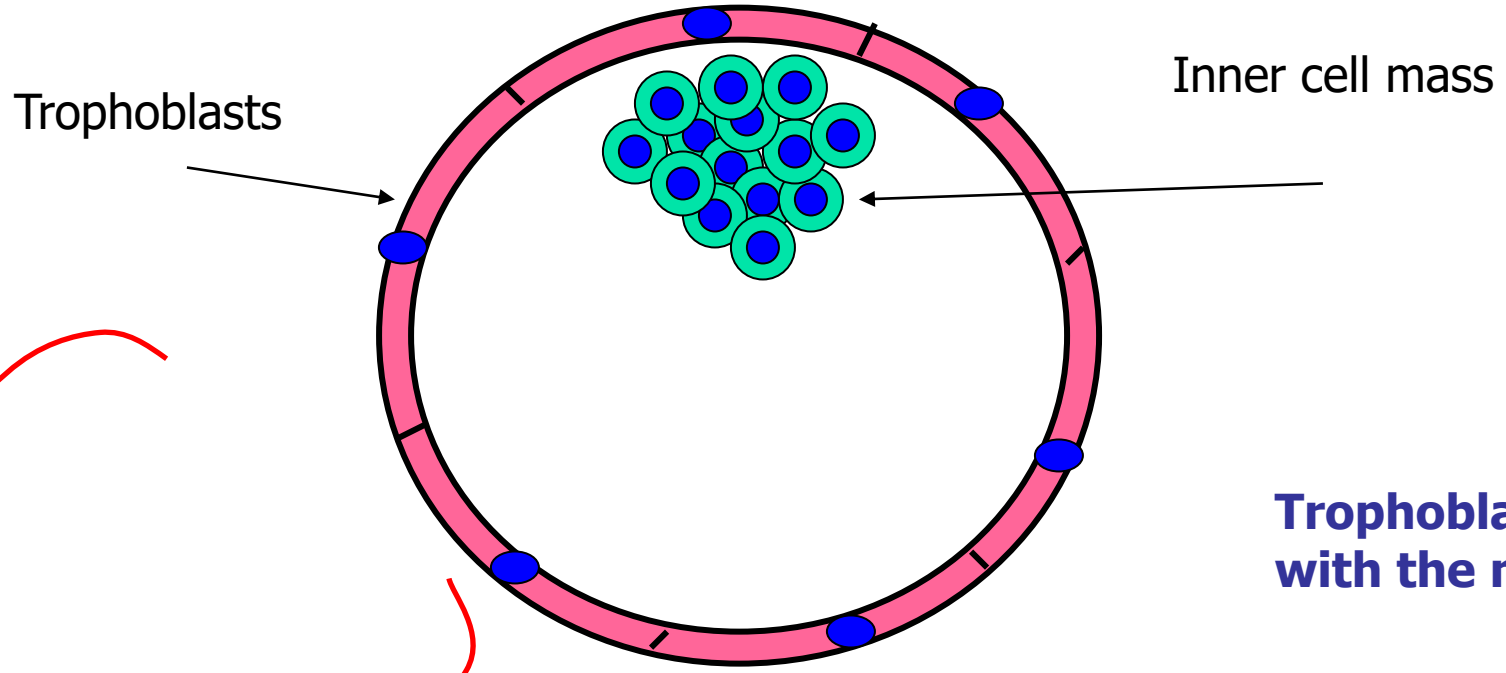
Morula = 16 cells +

Blastula = blastema and blastocoel

Blastocyst

Formation of Chorion

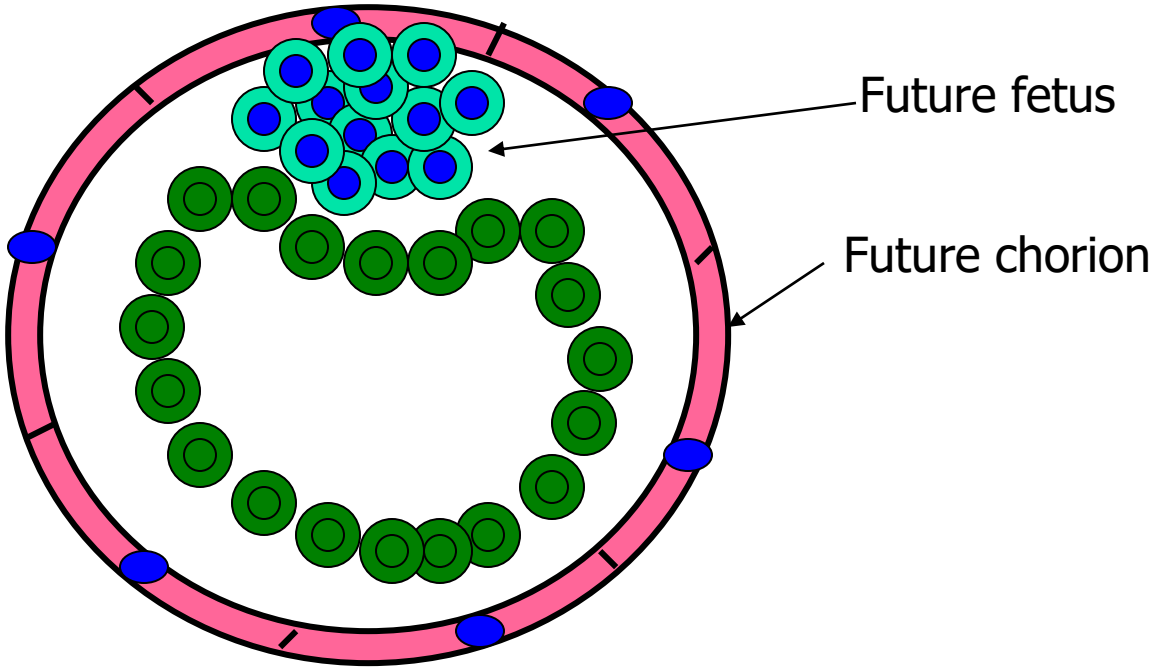
Chorion = Trophoblasts + mesoderm

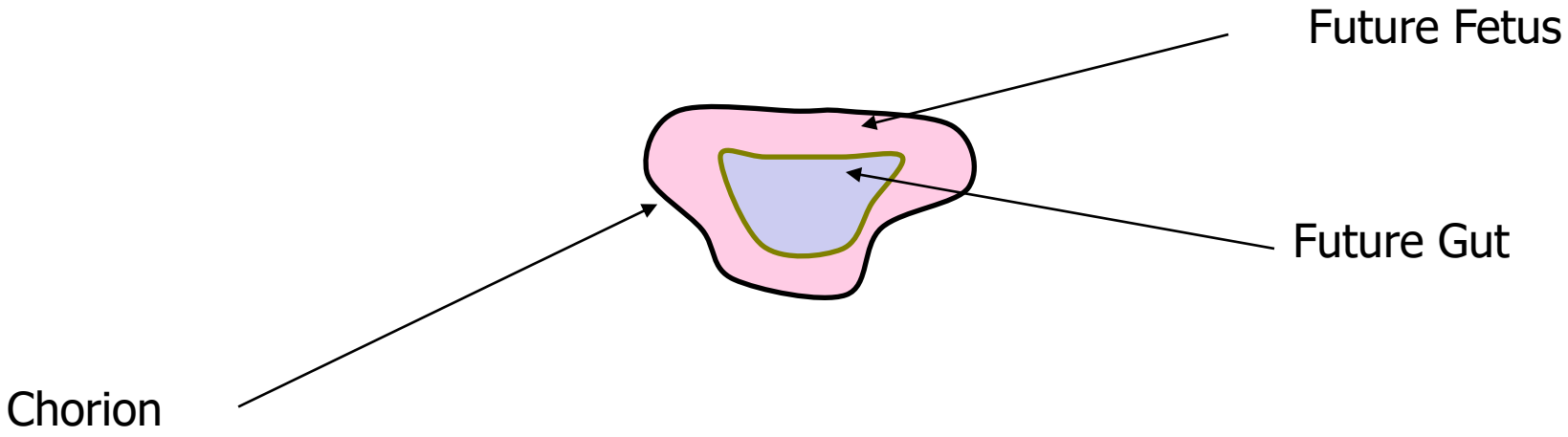


Trophoblasts are in contact with the mother

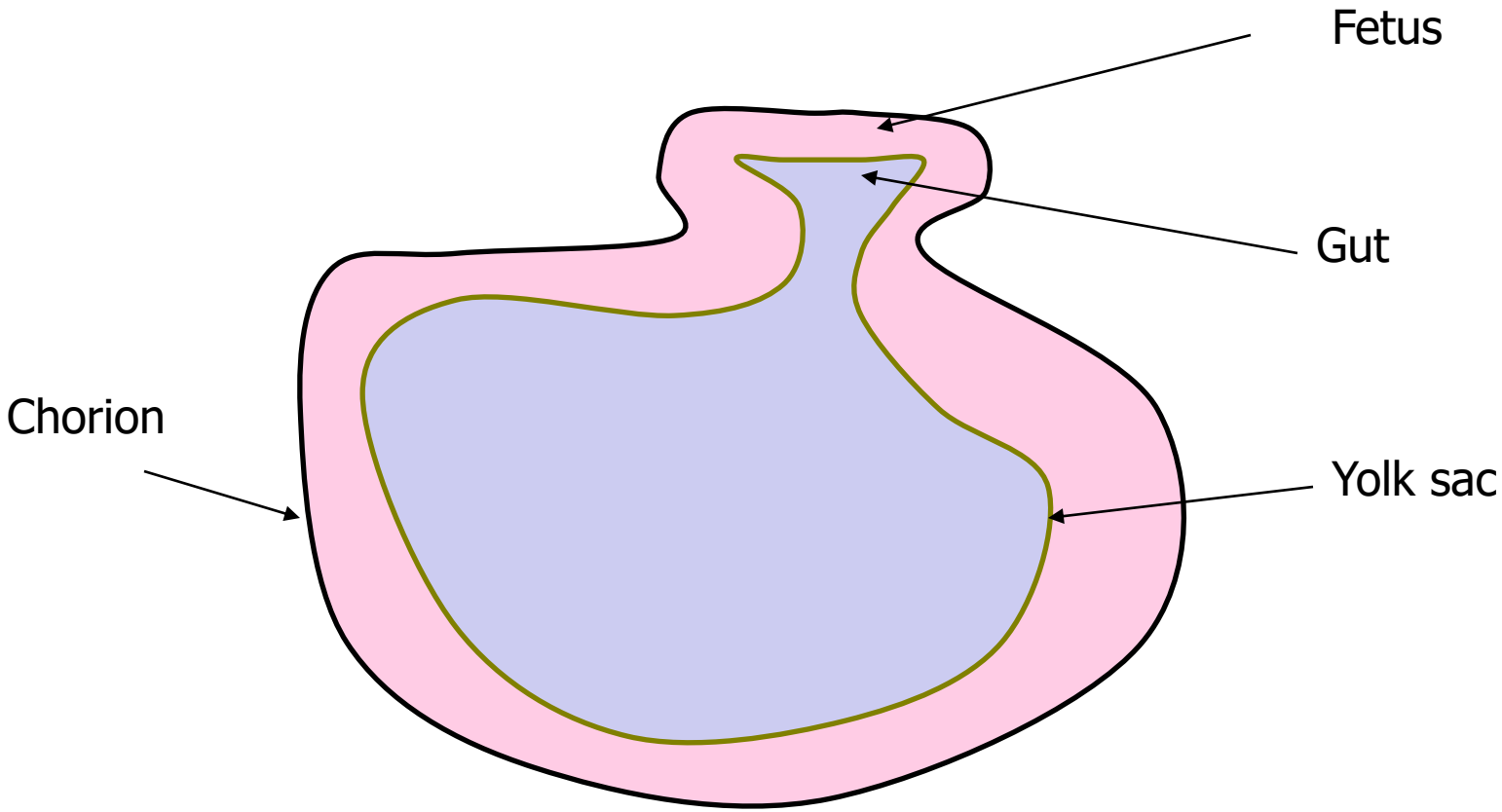
Formation of endoderm

- Endoderm = gut + yolk sac

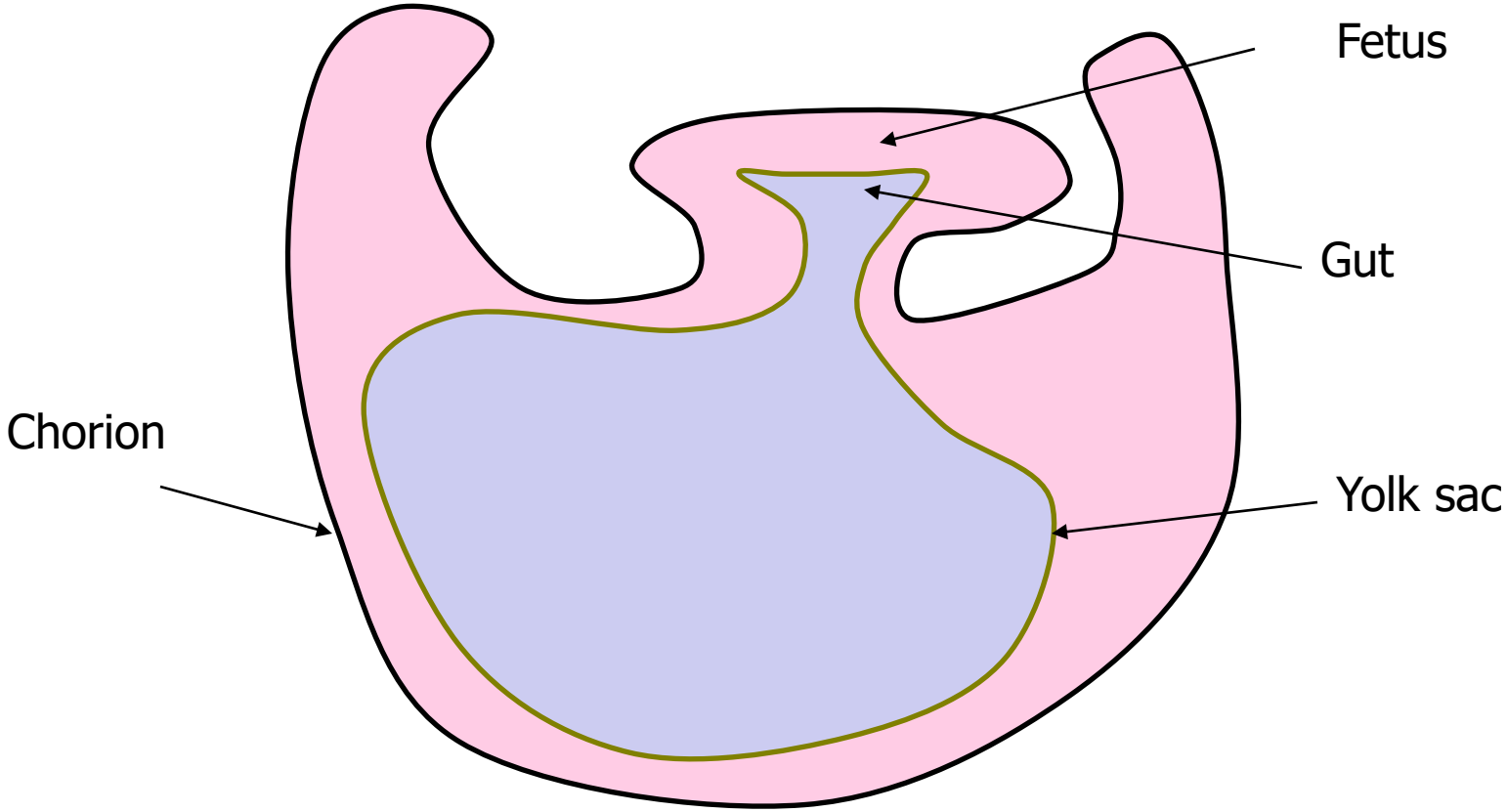



Future Fetus
Future Gut
Chorion

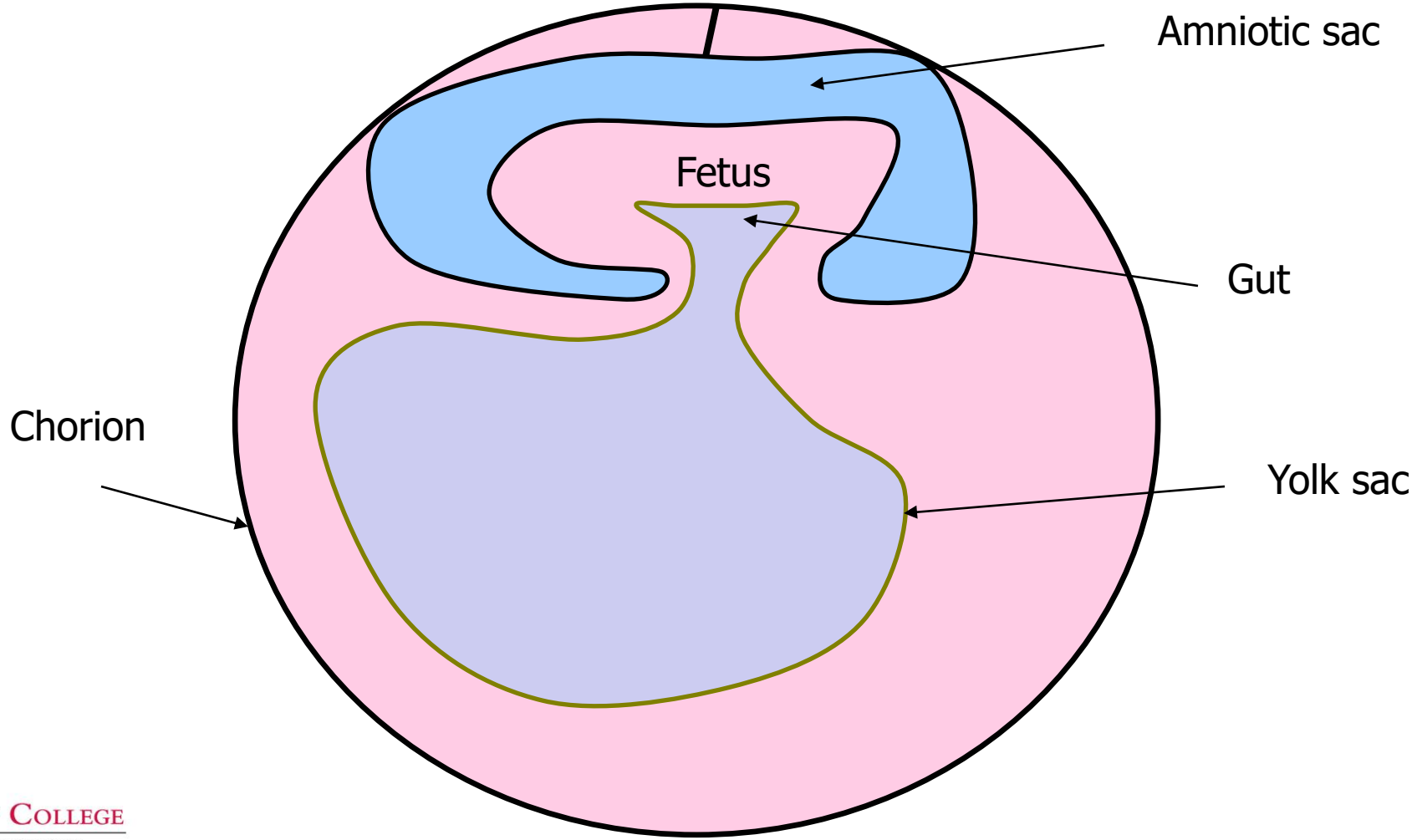
Formation of Yolk sac



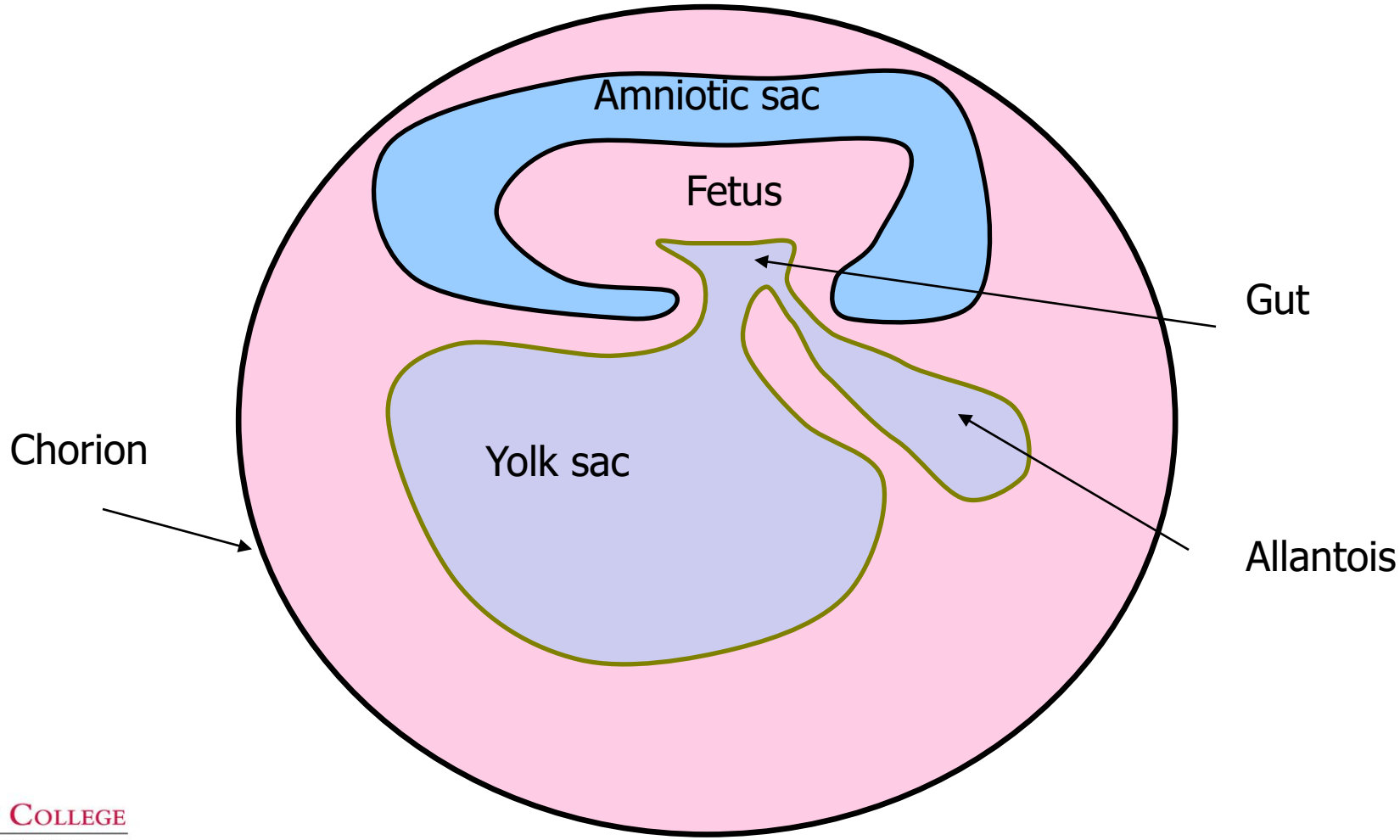
Formation of Amnion



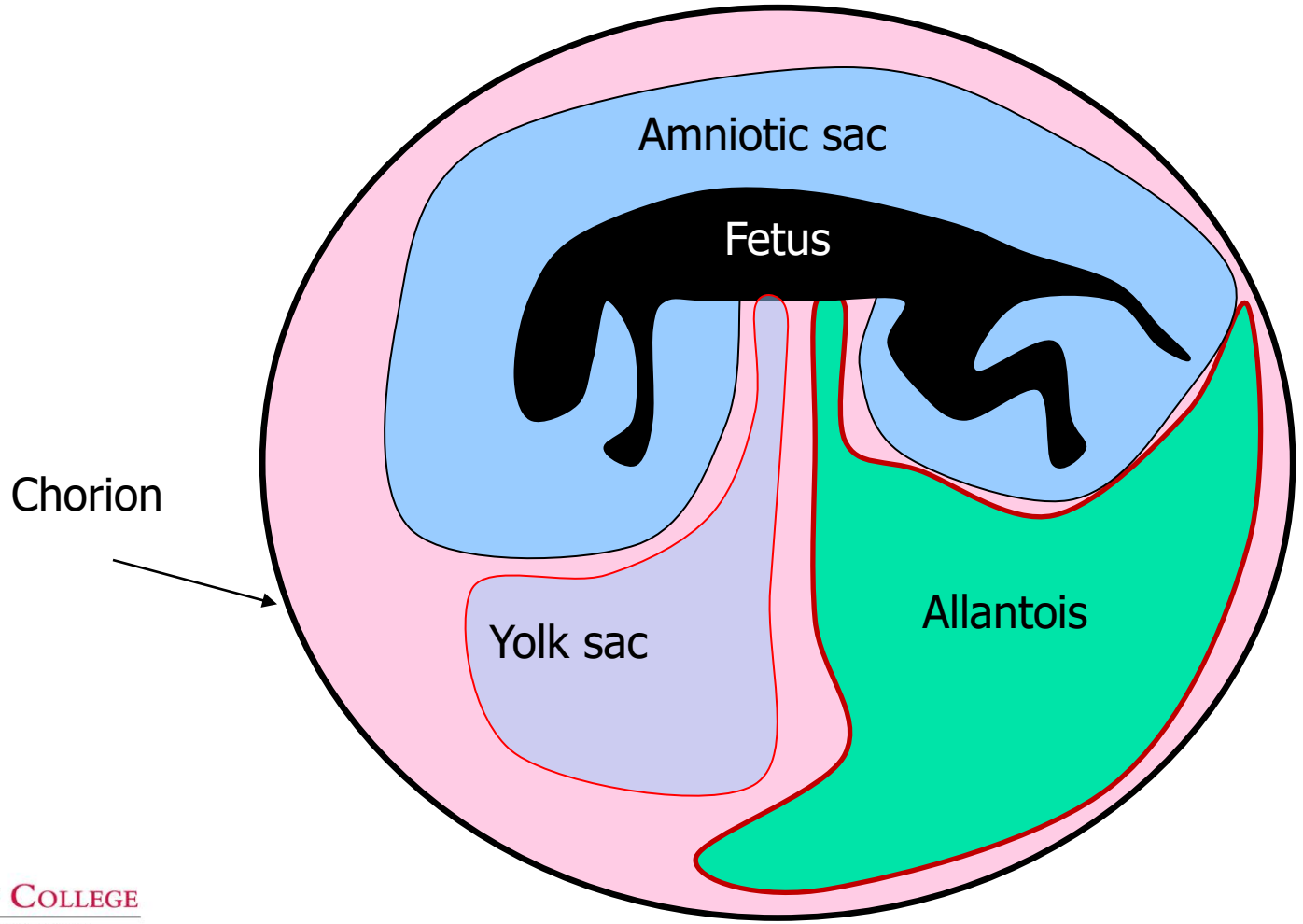
Formation of amnion



Formation of allantois



Formation of allantois

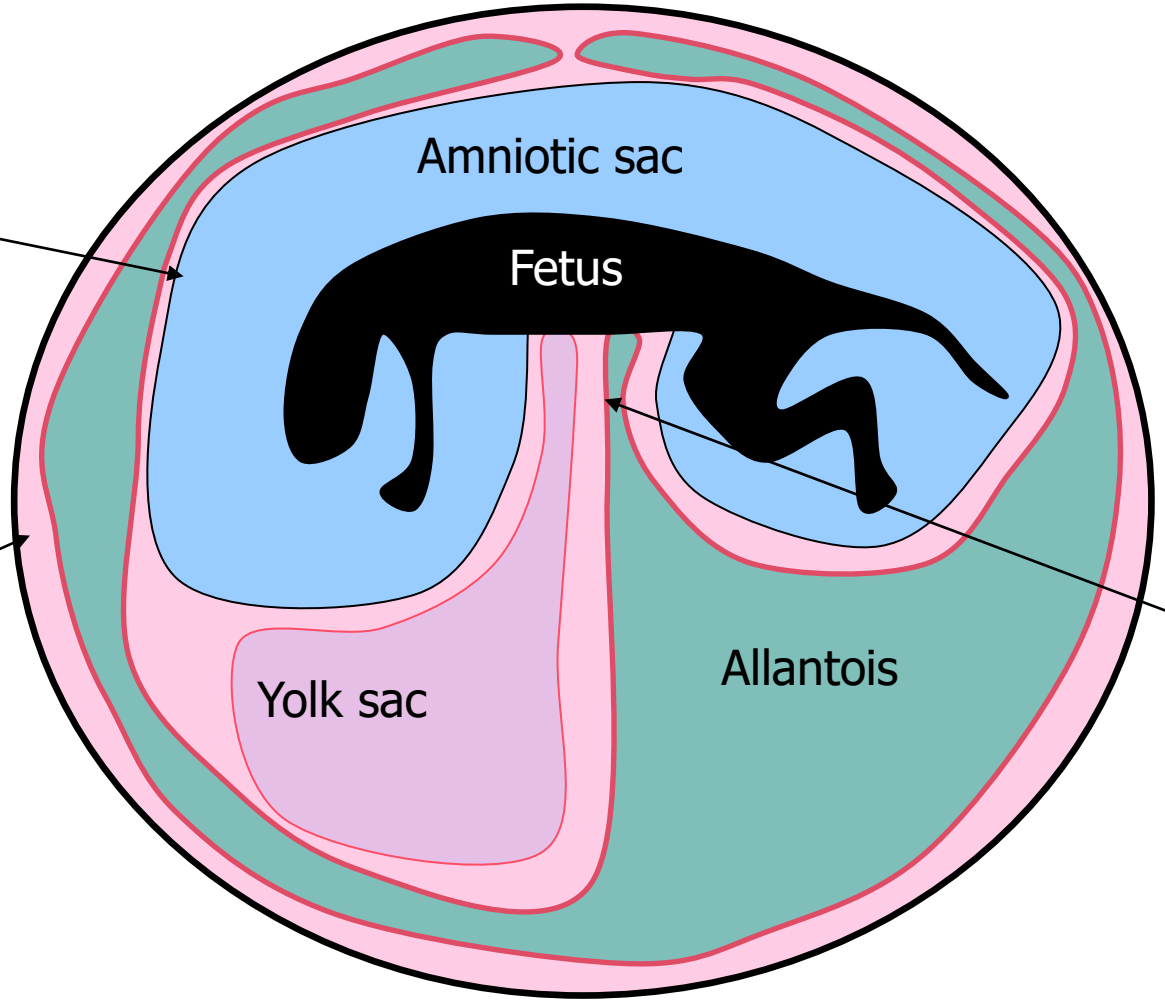


Formation of allantois

Membranes

Amniotic membrane

Chorioallantoic membrane



Umbilical cord = urachus, 2 arteries 1 vein

Vascular system of placenta

- Blood supply is high volume – low pressure

- Yolk sac prominent placentas
  - Marsupials
  - Rodents and lagamorphs
  - Carnivores
    - Allantoic vasculature takes over later

Horse

Endometrial surface with embryo

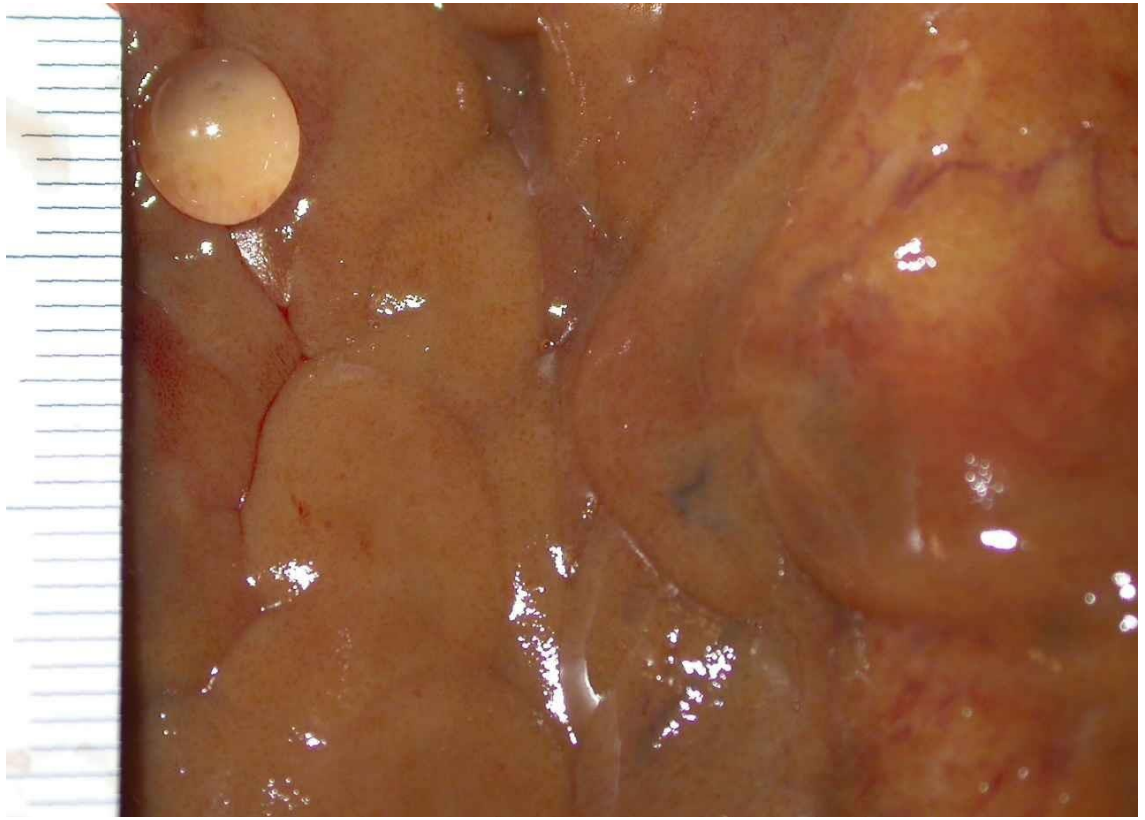
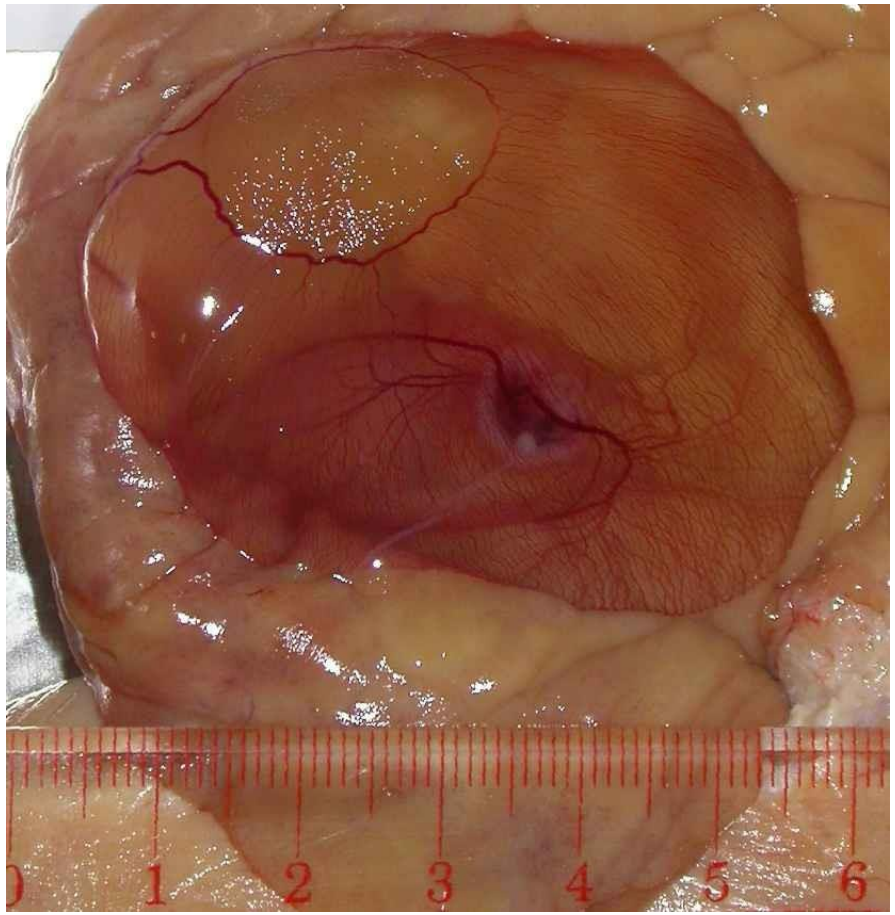


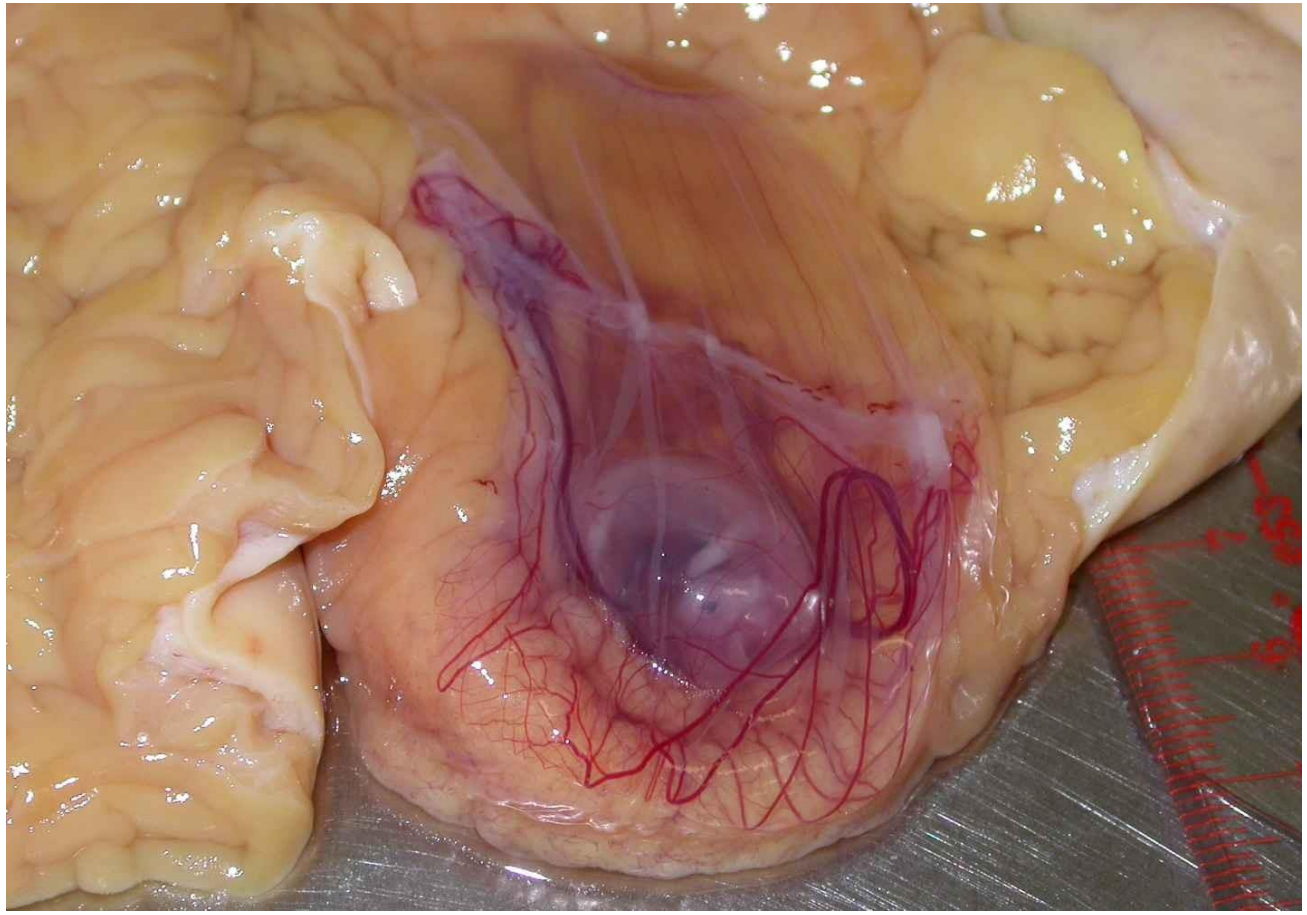
Photo courtesy Dr Tony Hayes

Horse



Photograph courtesy Dr Tony Hayes

Horse



Photograph courtesy Dr Tony Hayes

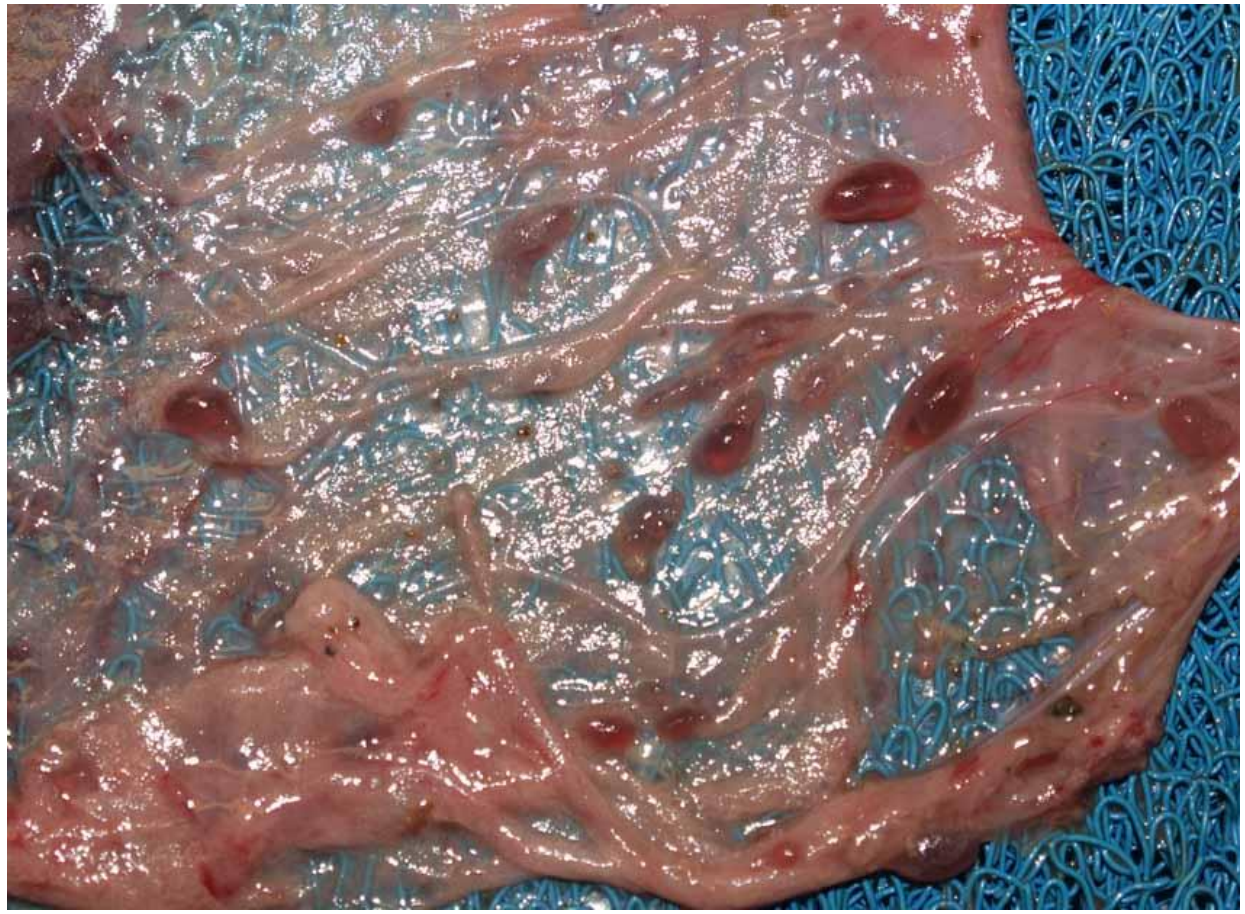
Placental structures

- Chorion and arrangement
  - Pig – villus – uterine milk - histotroph
  - Equine – microcotyledonary – uterine milk - histotroph
  - Ruminant – cotyledonary - haemotroph
  - Carnivore – zonary - haemotroph
- Allantoic cavity and membrane
- Amniotic cavity and membrane
- Umbilical cord and components

Umbilical cord

- 2 arteries – umbilical arteries from iliac arteries
- 1 vein – umbilical vein to ductus venosis
- Urachus – from bladder to allantois

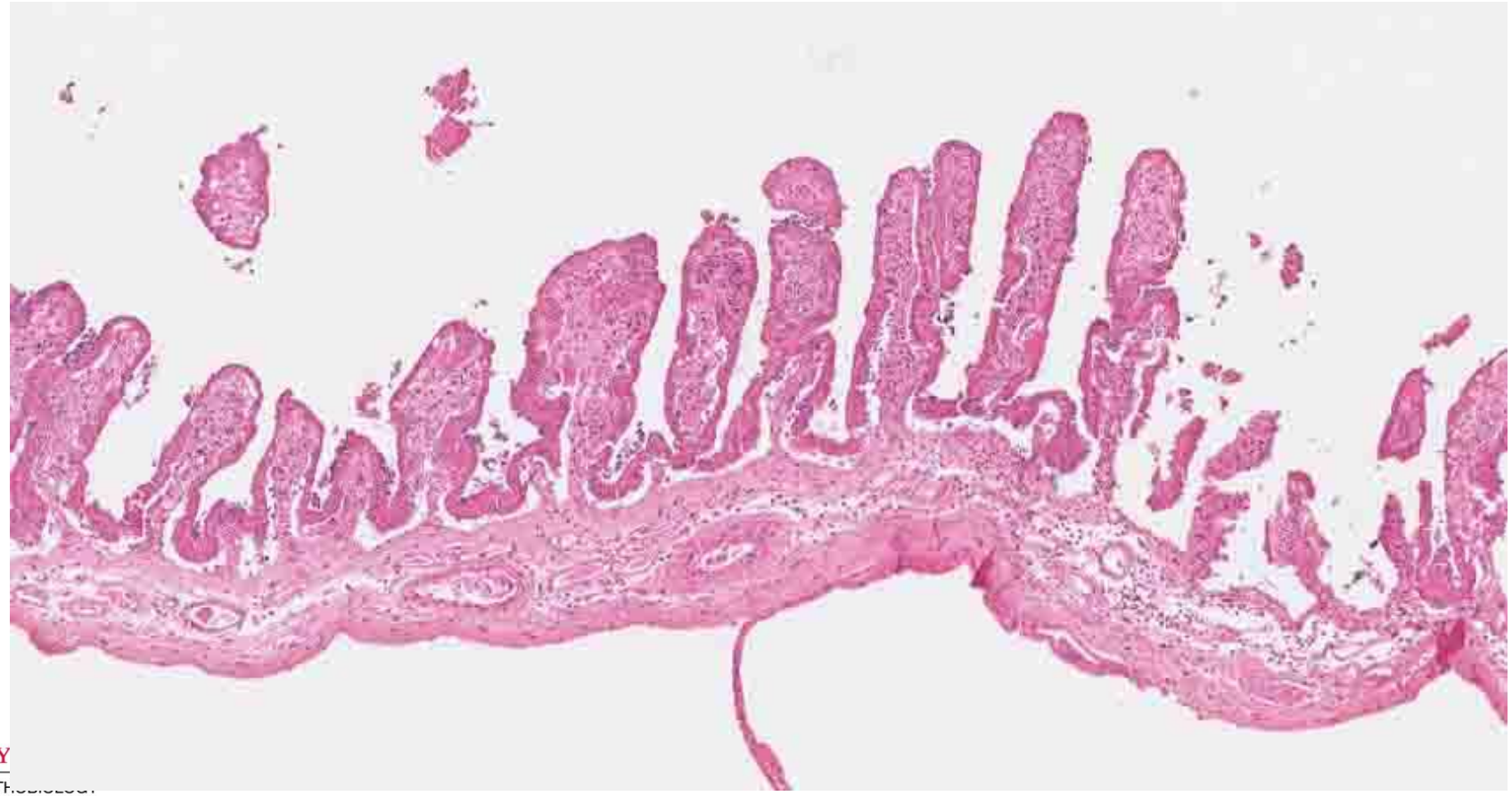
Porcine placenta



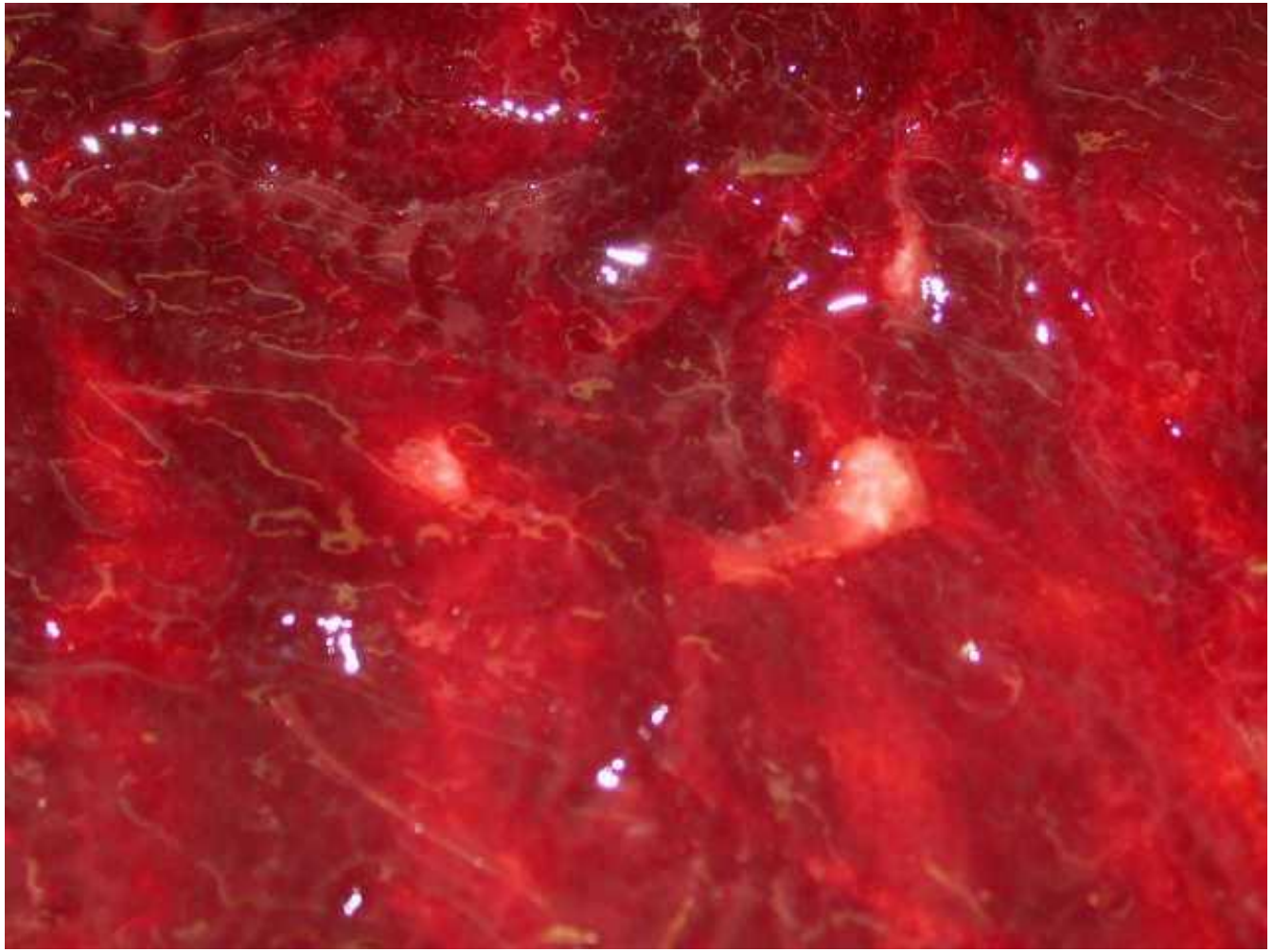
Chorionic cysts

Porcine placenta

Villi



Equine placenta

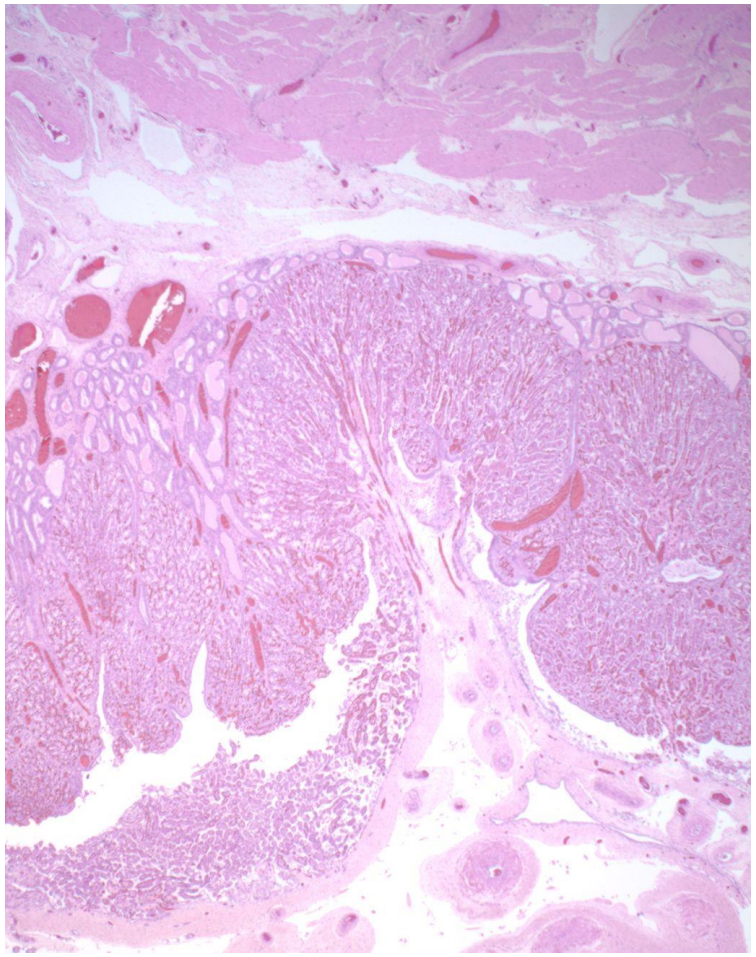


Equine placenta

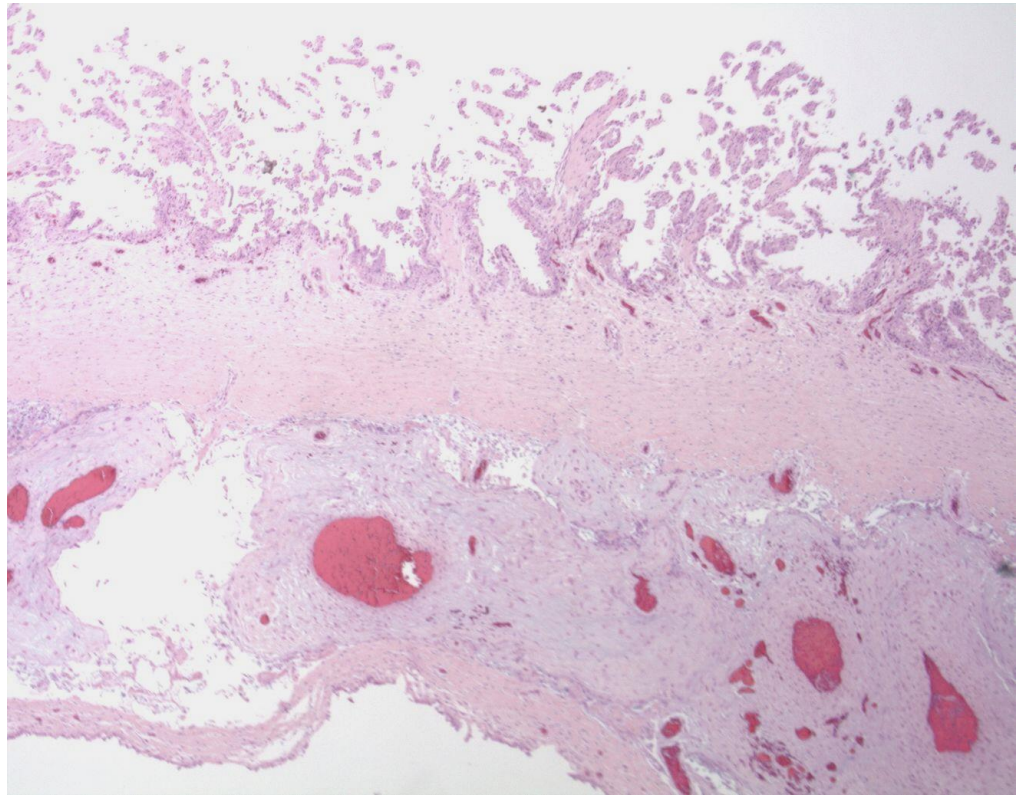
Uterus

Endometrial glands

Chorioallantois



Microcotyledonary



Chorioallantois

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Ruminants – placentomes

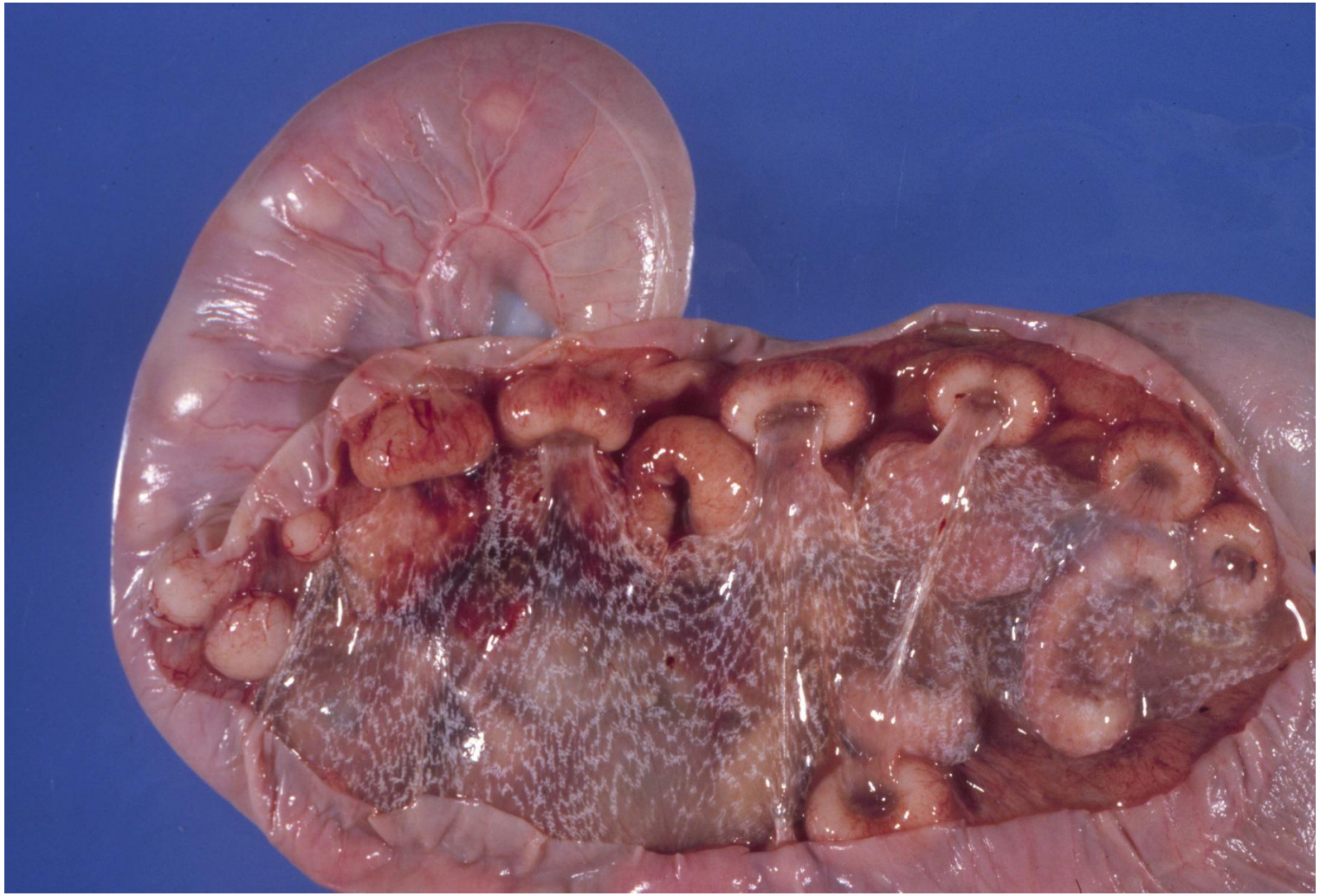
- Caruncle (maternal)

Photograph complement of the Holden Racing Team

- Cotyledons (fetal)

www.fungiforays.co.uk

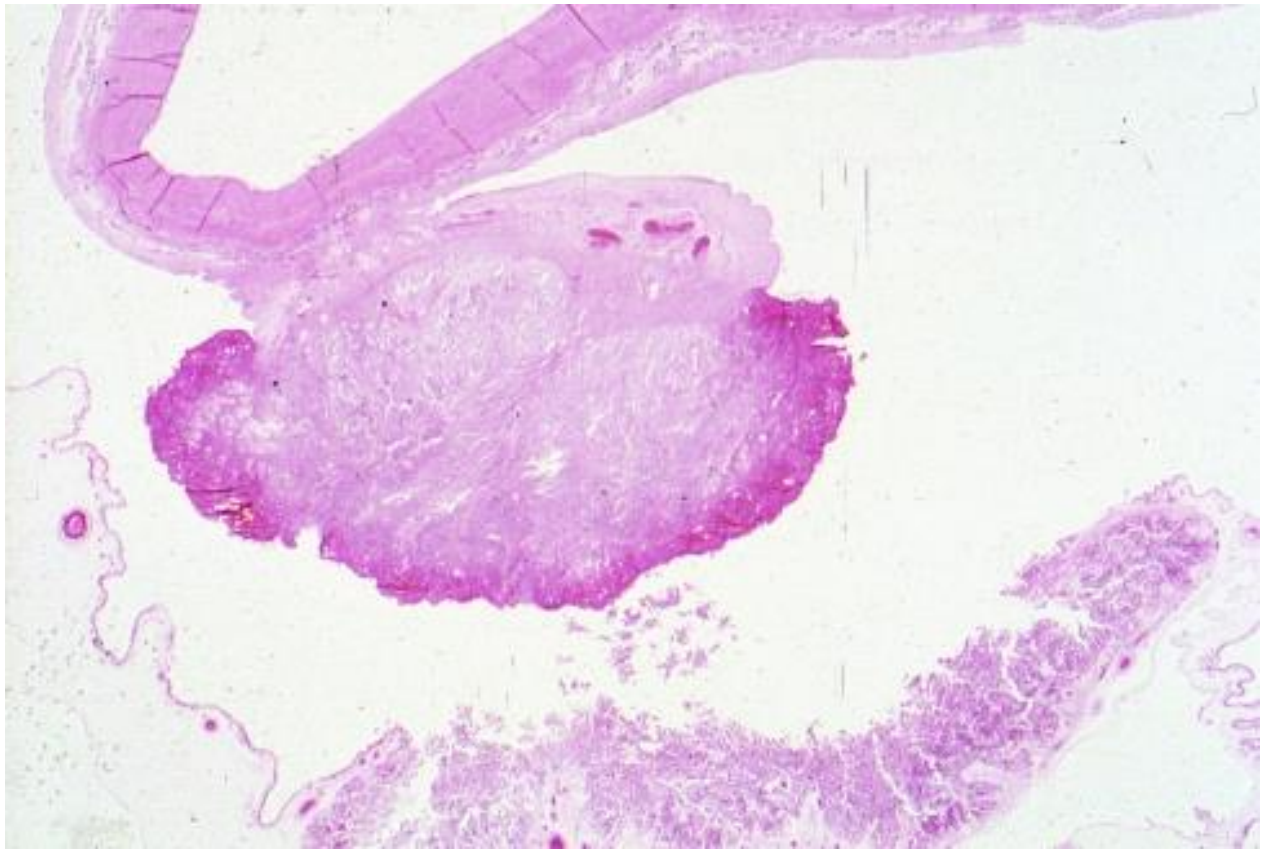
Ruminant



Bovine placentome

Uterus

Caruncle

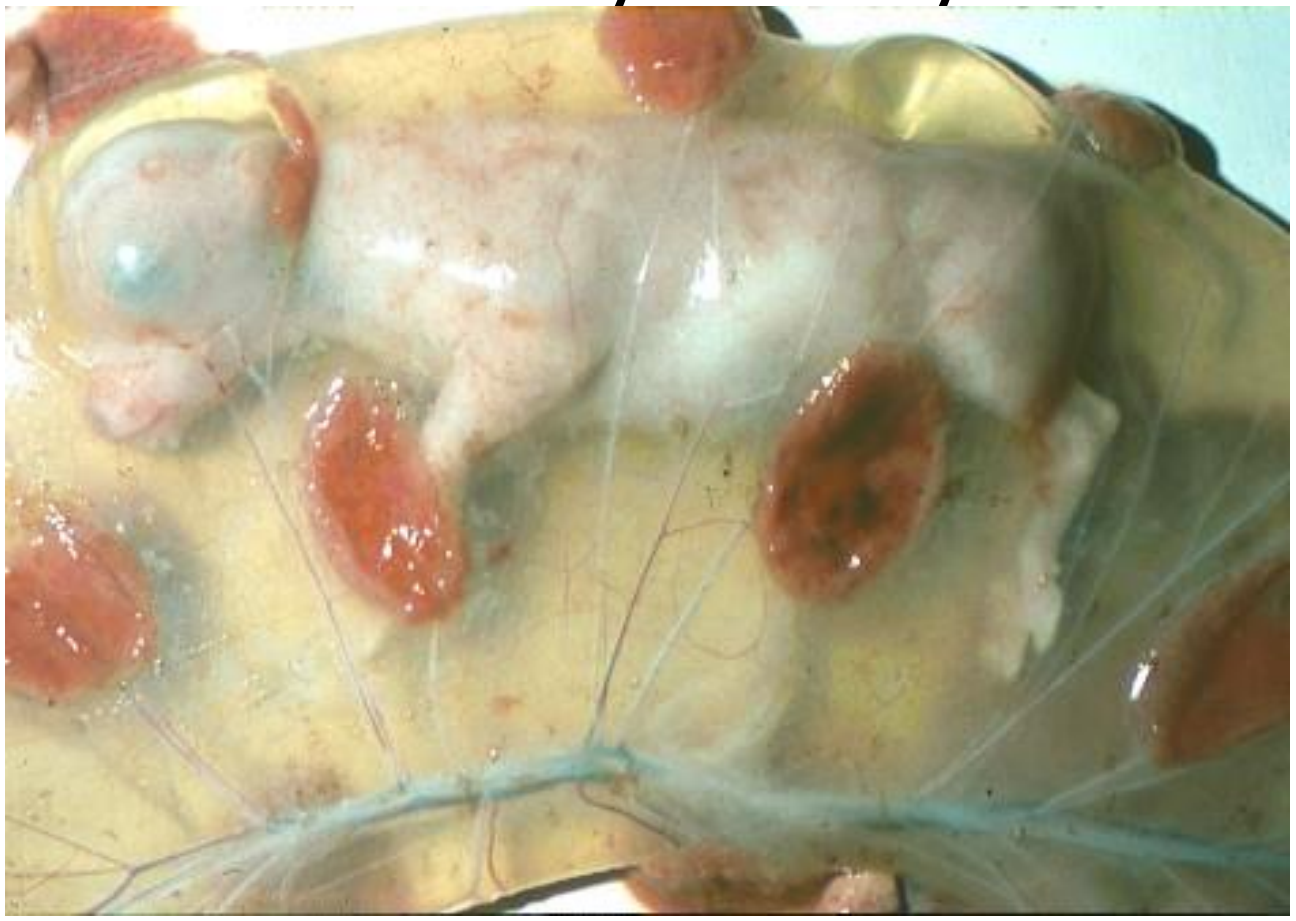


Cotyledon

Chorioallantois

Ruminants

Cotyledonary

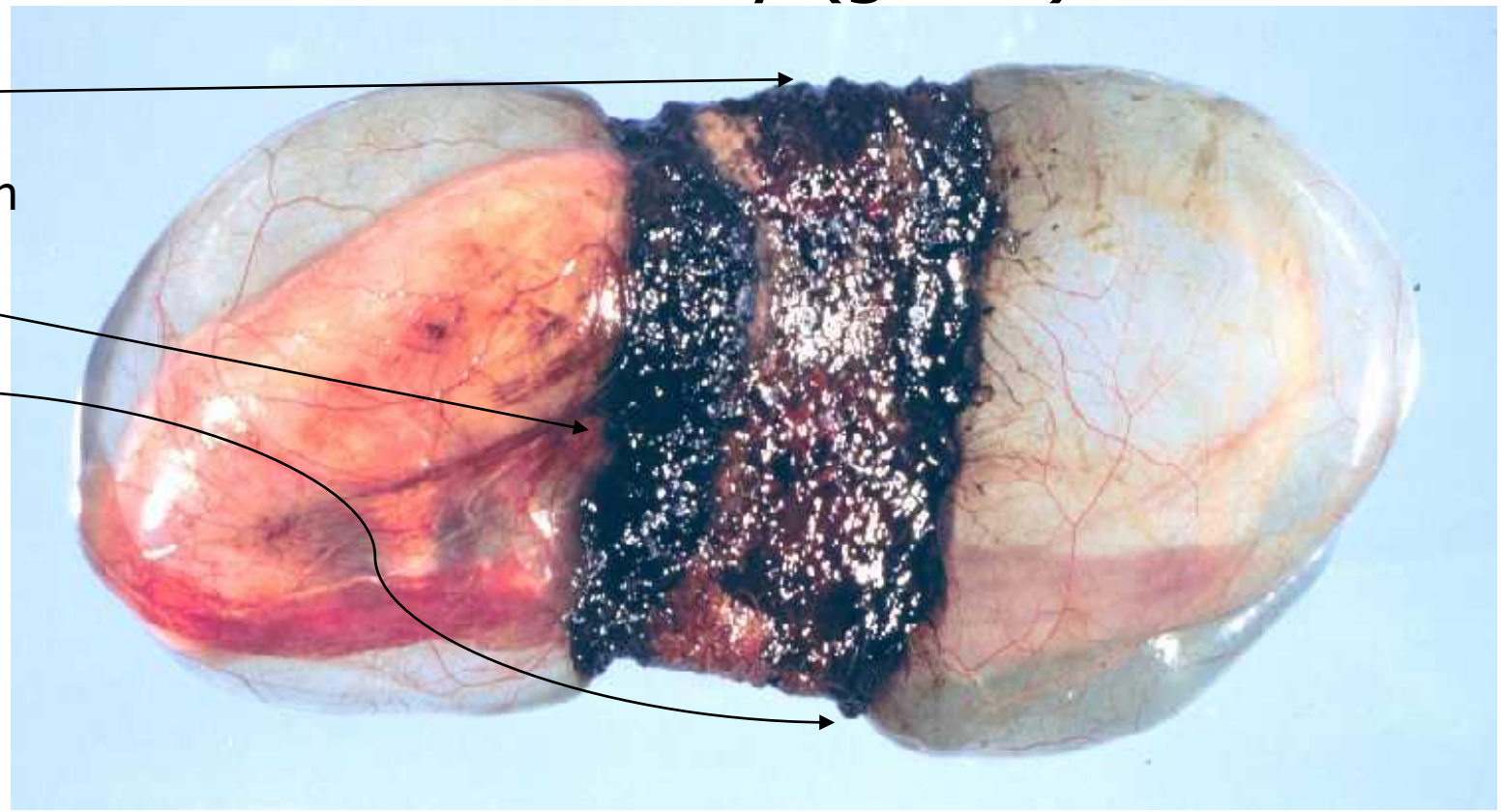


Carnivore

Zonary (girdle)

Labyrinth

Marginal hematomas on each side of labyrinth



Remnants

- Meckels diverticulum – small intestine – yolk sac
- Omphalomesenteric bands
- Yolk sac remnant in horse
- Persistent urachus
- Round ligaments of bladder (umbilical arteries)
- Falciform ligament (umbilical vein)

Placental structures

- Chorion and arrangement
  - Porcine
  - Equine
  - Ruminant
  - Carnivore
- Allantoic cavity and membrane
- Amniotic cavity and membrane
- Umbilical cord and components

General Causes of Failure of Pregnancy

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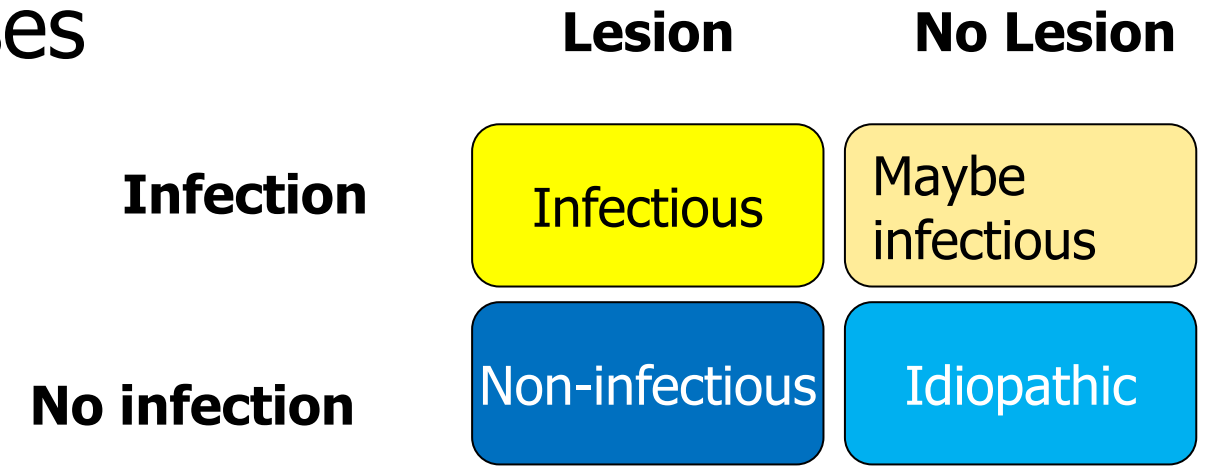
Parallel approaches to FOP

- Fetal causes
- Placental causes
- Maternal causes
- Paternal causes
- AND



Abortogenic/uterotropic agents common to all species

- Bacteria
  - *Brucella*
  - *Campylobacter*
  - *Leptospira*
  - *Listeria*
  - *Salmonella*

  - *Chlamydia*
  - *Coxiella*
  - *Mycoplasma*
  - *Ureaplasma*
- Fungi
  - *Aspergillus fumigatus*
- Protozoa
  - *Neospora caninum*
  - *Toxoplasma gondii*
- Viruses
  - *Simplexvirus:* alphaherpesviruses

Utero = womb or belly; -tropic from Greek Tropicus - belonging

Stages of pregnancy and failure

- Embryonic mortality
  - conceptus, embryo
- Abortion
  - fetus
- Maceration
- Mummification
- Stillbirth

Causes of Embryonic Death

- Infectious
  - Usually see early embryonic mortality
  - Specific pathogens
  - Nonspecific pathogens – post partum or post breeding endometritis

- Noninfectious
  - Usually see late embryonic mortality
  - Chromosomal abnormalities
  - Genetic anomalies - living cattle have traits that are heterozygous only!
  - Twinning
  - Summer heat/seasonal infertility
  - Suboptimal progesterone (cows, dogs, horses)
  - Alteration of immune profile.

Determine Cause of Abortion and Stillbirth

- Clinical history and interview
- Take precautions to prevent zoonotic disease
- Determine common diseases
- Examine Mother, Fetus and Placenta
  - Lesions to explain the failure of pregnancy
- Diagnostic testing
    - Infectious or not
    - adequate examination
    - non infectious / management
- Final diagnosis

Maternal Disease

This is for clinicians

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Disease of Fetus

Examination of the fetus

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Ontario Veterinary College
Department of Pathobiology

Examination of the fetus

- **Has fetal growth and development been normal (how?)**
  - nutrition
  - placental sufficiency
  - fetal disease or anomaly
- **Time of death prior to expulsion**
- Fetal distress
- Dystocia - swelling of head

Time of Death based on sheep experiments

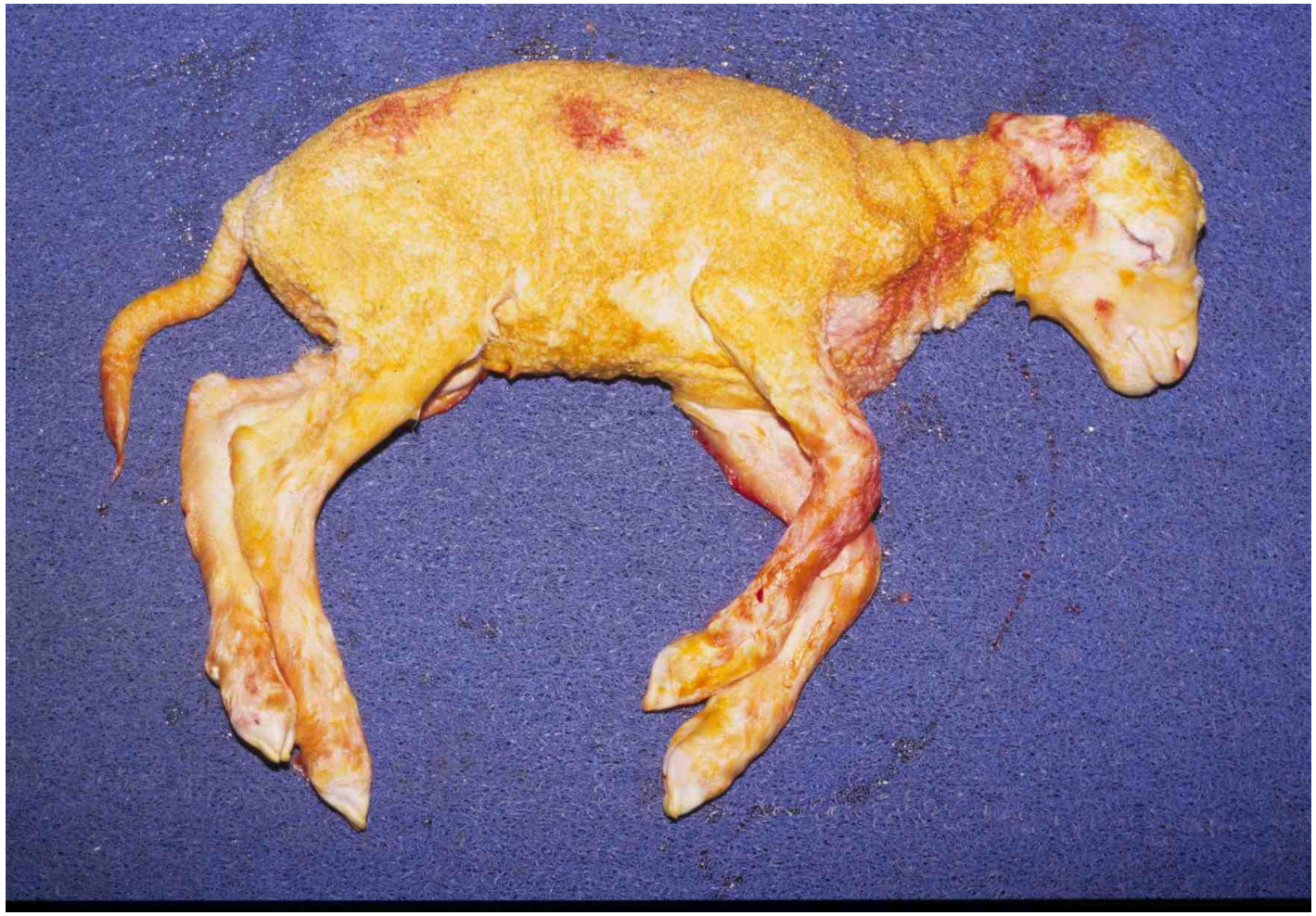
- 12 hr — cornea cloudy
- 24 -36 hr — bloody fluid in cavities
- 72 hr — dehydration begins
- 144 — mummification

Examination of the fetus

- Has fetal growth and development been normal (how?)
  - nutrition
  - placental sufficiency
  - fetal disease
- Time of death prior to expulsion
- **Fetal distress**
- Evidence of dystocia

Dys = bad; Tokus - childbirth

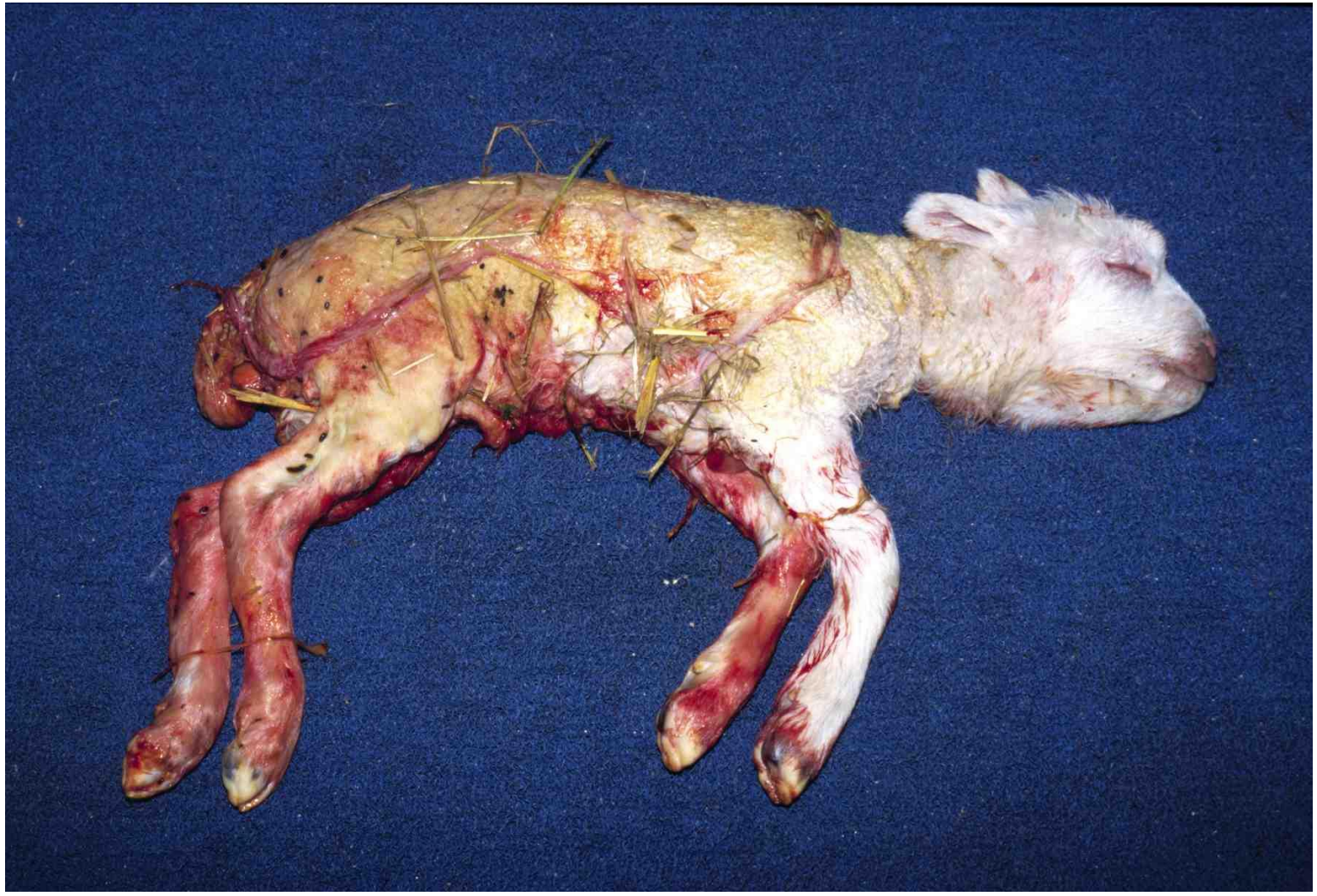
Sheep: Meconium staining



Examination of the fetus

- Has fetal growth and development been normal (how?)
  - nutrition
  - placental sufficiency
  - fetal disease
- Time of death prior to expulsion
- Fetal distress
- **Evidence of dystocia**

Sheep: Dystocia

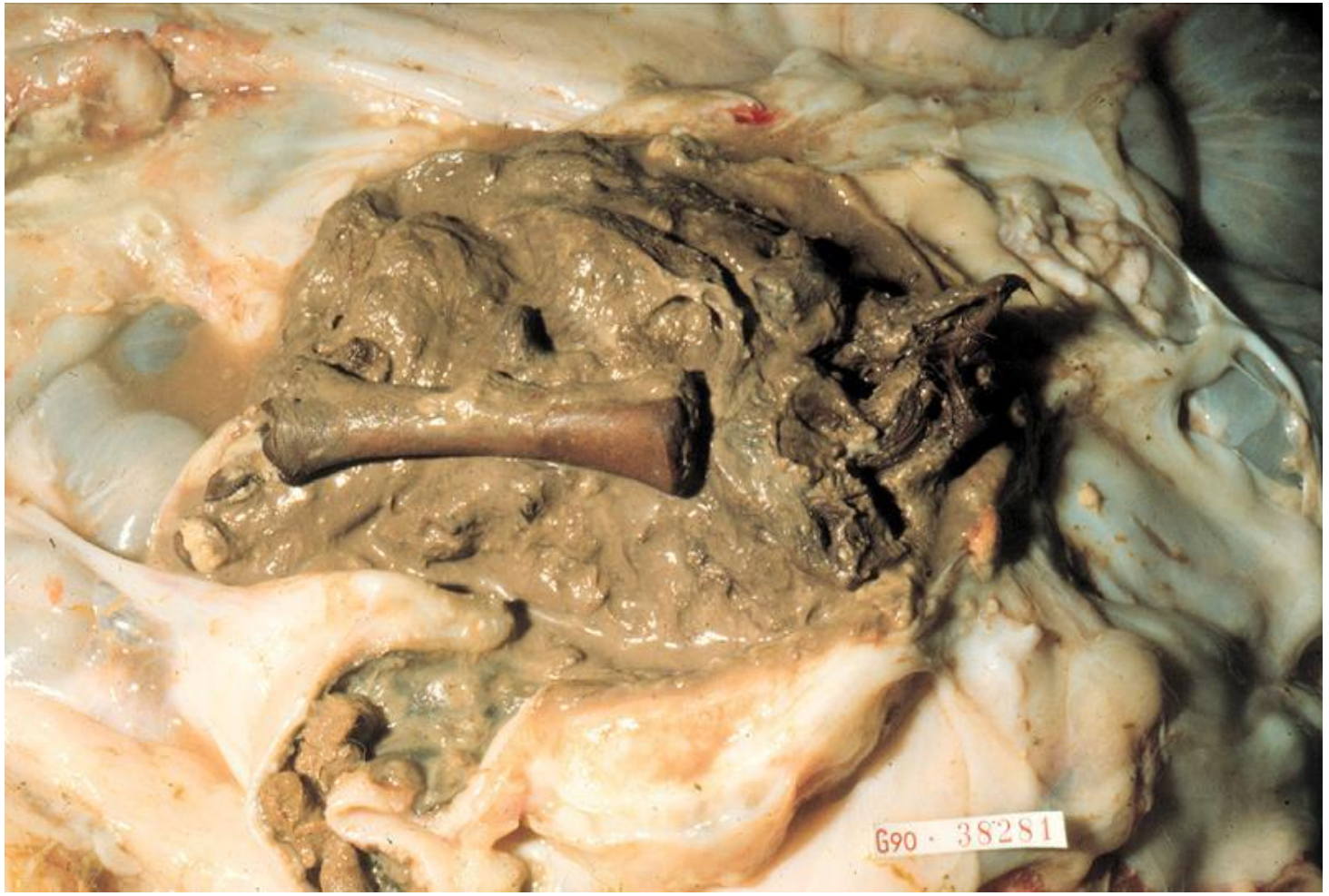


Pig: Mummification

- Horse - twinning
- Cow – *Pestivirus* A, B (BVDV) infection
- Cat - torsion of uterine horn
- Dog - *Canid alphaherpesvirus 1*
- Pig – *Ungulate protoparvovirus* (Porcine parvovirus)

Mummify = to dry or shrivel up

Sheep: Maceration



Macerate = to soften or separate into parts by steeping in a liquid.

Placental Disease

Examination of the placenta

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Equine Failure of Pregnancy

Examination of failure of pregnancy in horses is the most rewarding of all species.

Placental examination is very calming (wellness plus)

Equine FOP truisms…

- many ‘nonlesion’ lesions – know them.
  - Normal or incidental placental structures
- ‘no’ placental reserve so look carefully.
  - I question this.
- ‘loose’ cervix
  - Ascending infection and endometritis is common
  - Intrauterine insemination – contamination and post breeding endometritis

Functional Anatomy of Equine Uterus and Placenta

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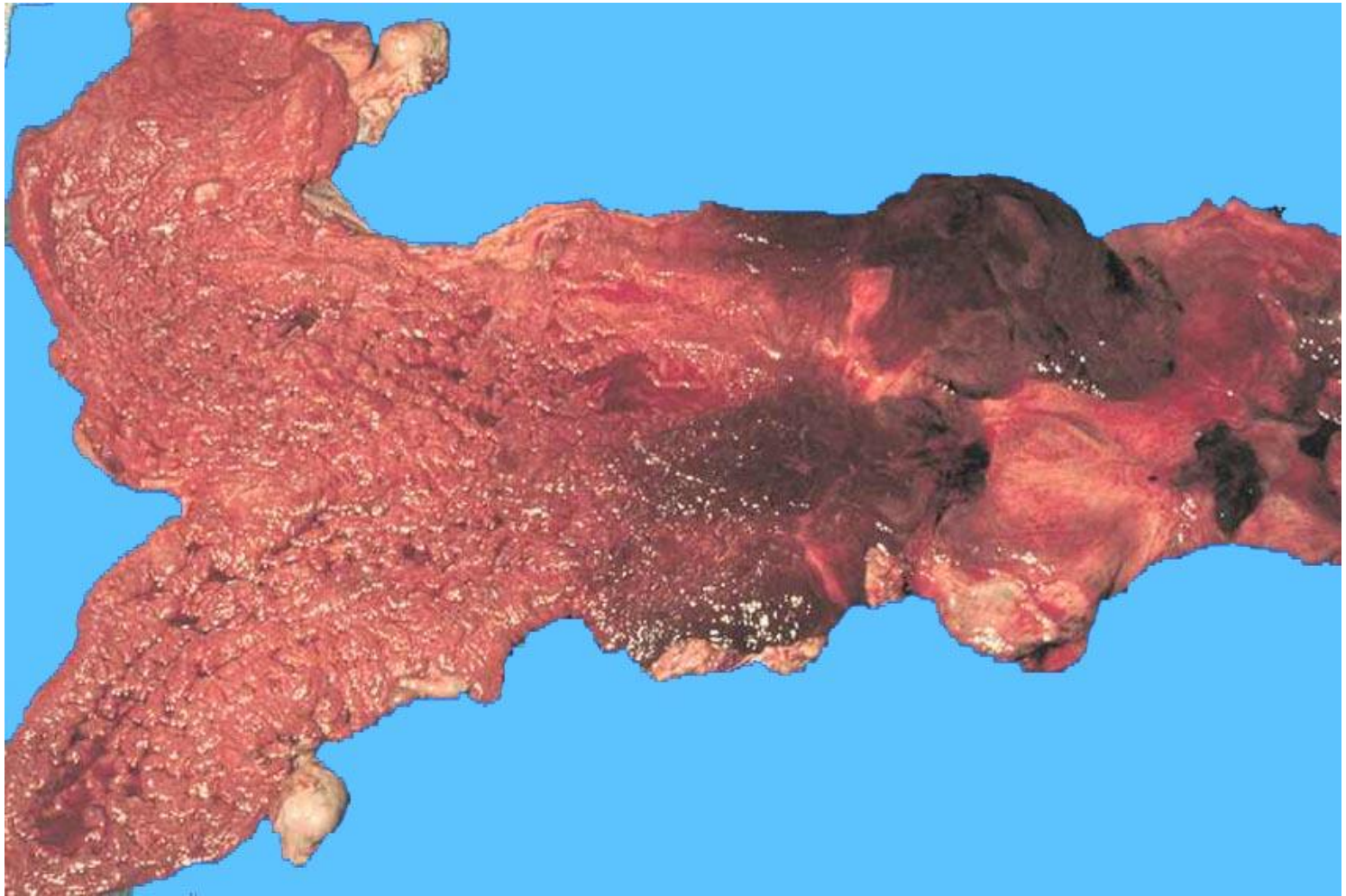
Horse: Normal uterus

Horse: Postpartum uterus



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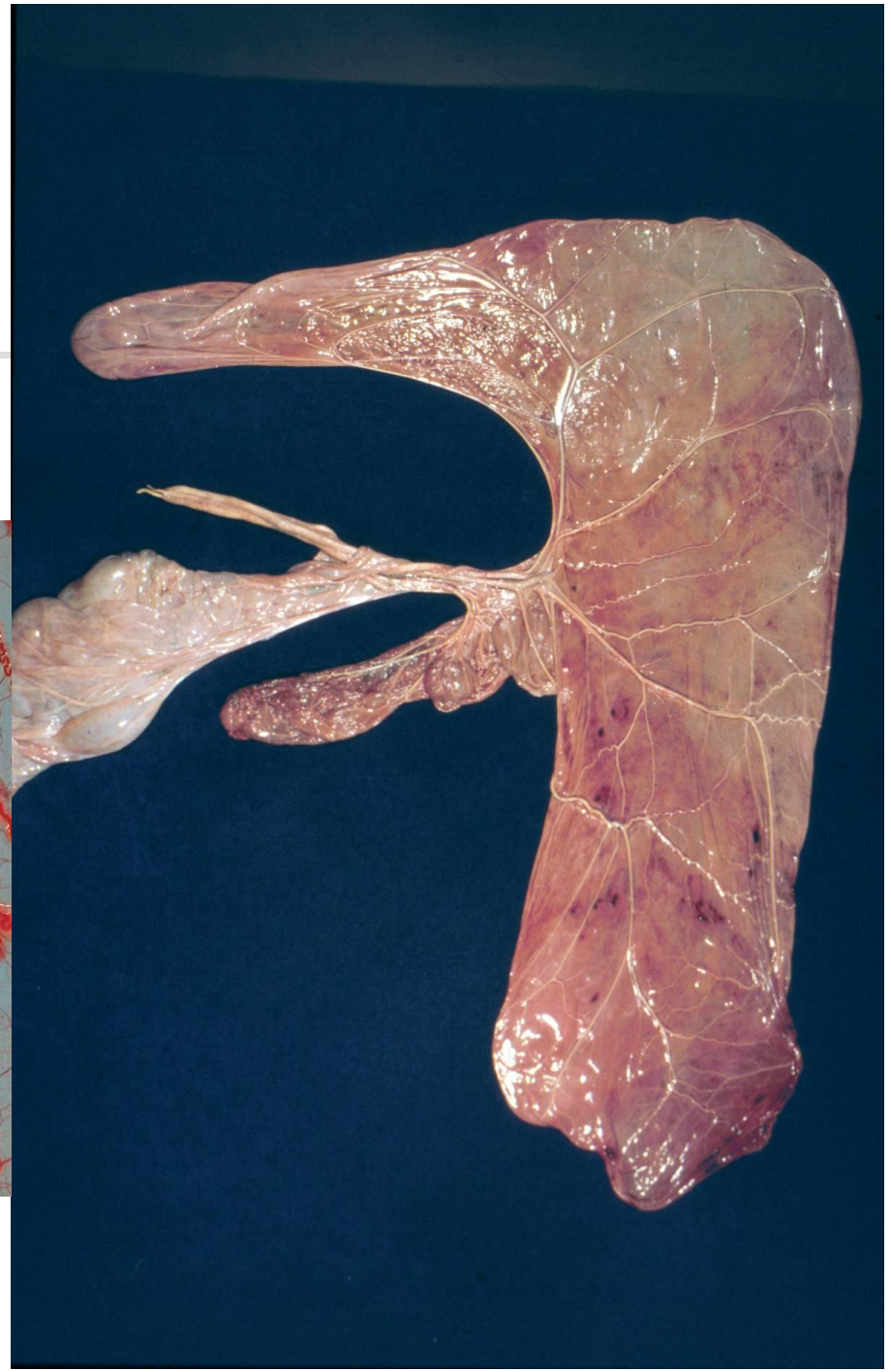
Horse: placenta

- Lay out placenta (F or Y)
- Recognise
  - Pregnant horn
  - Nonpregnant (front leg) horn
  - Body
  - Cervical star
  - Site of rupture at cervical star
  - Side of insertion of cord
  - Side of pregnancy

Internal surfaces

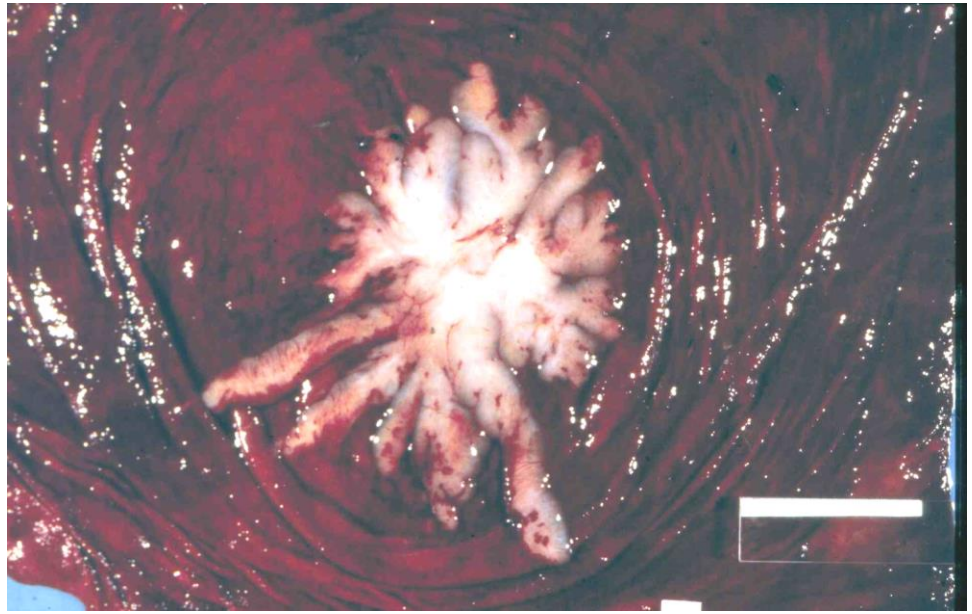
Recognise

- Allantoic cavity
- Amnion
- Umbilical cord
  - Side of attachment
  - Length
  - 2 arteries, 1 vein
  - Excessive twists
  - Marvel at blood vessels

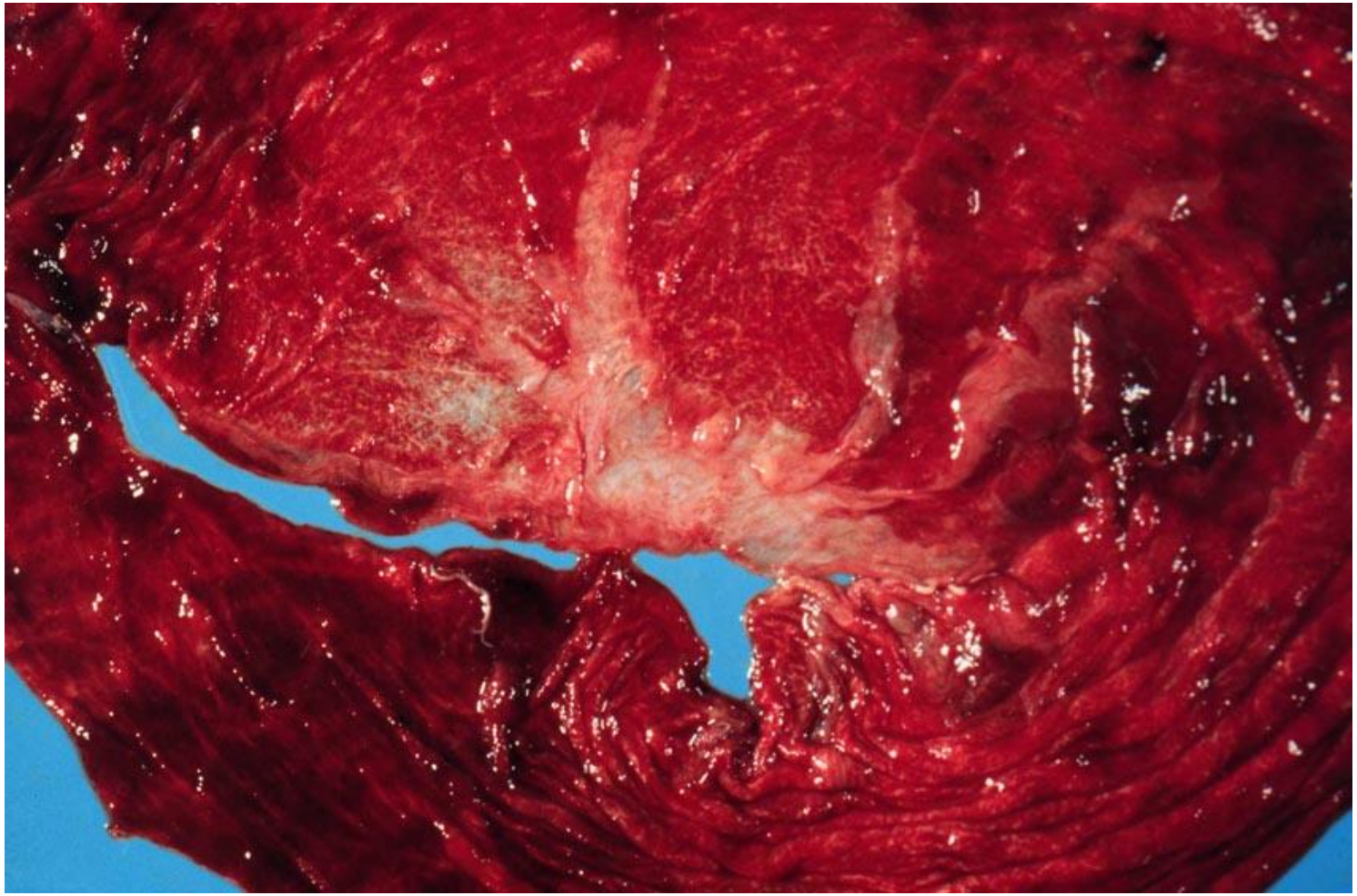


Nonlesion lesions

- Avillous regions
  - **cervical star**
  - chorioallantoic pouch
  - insertion of cord
- Allantoic pouches
- Yolk sac remnant
- Hippomane
- Fetal autolysis



Postpartum cervical star



Nonlesion lesions

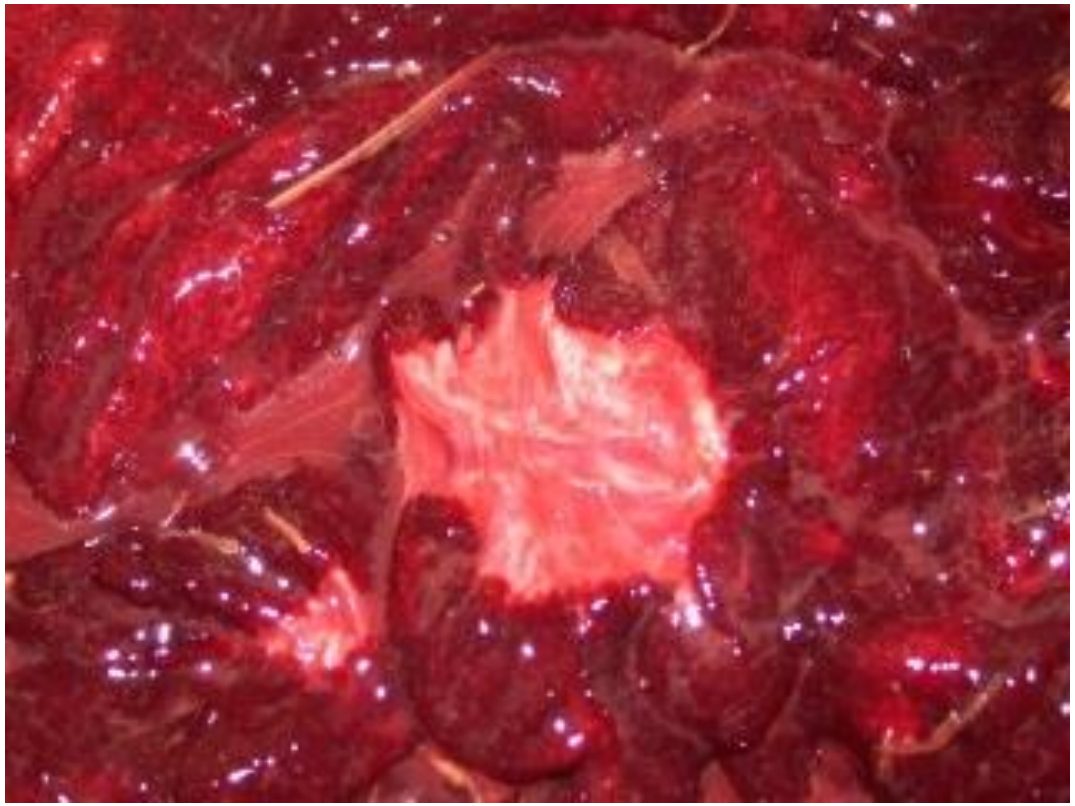
- Avillus regions
  - cervical star
  - **chorioallantoic pouch**
  - Insertion of cord
- Allantoic pouches
- Yolk sac remnant
- Hippomane
- Fetal autolysis

Endometrial cups

Chorioallantoic pouch

Nonlesion lesions

- Avillus regions
  - cervical star
  - chorioallantoic pouch
  - **Insertion of cord**
- Allantoic pouches
- Yolk sac remnant
- Hippomane
- Fetal autolysis

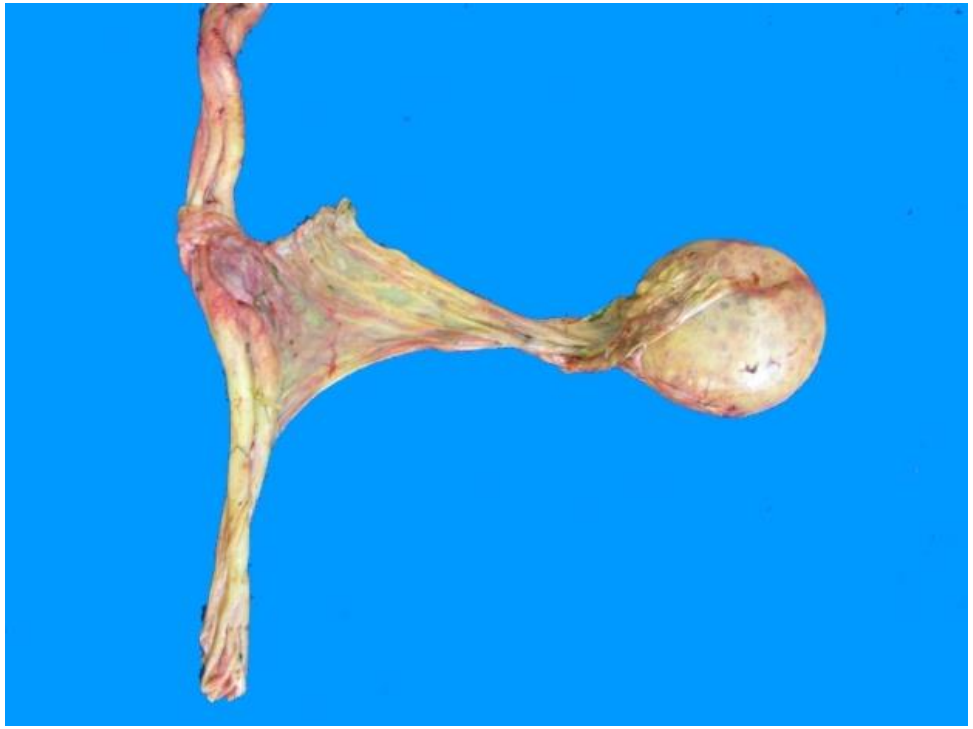


Nonlesion lesions

- Avillous regions
  - cervical star
  - chorioallantoic pouch
  - insertion of cord
- **Allantoic pouches**
  - **Polyp/vesicle**
- Yolk sac remnant
- Hippomane
- Fetal autolysis

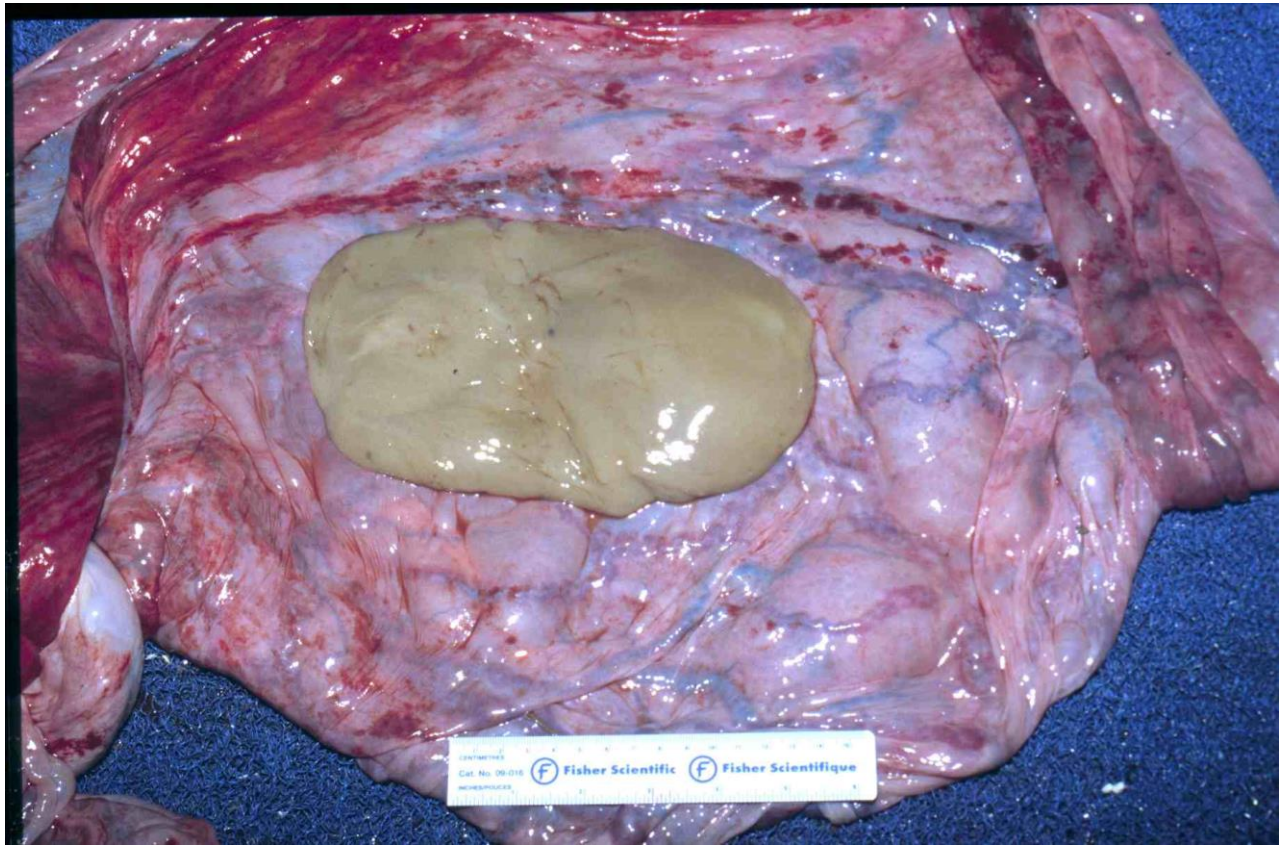
Nonlesion lesions

- Avillous regions
  - cervical star
  - chorioallantoic pouch
  - chorionic fold
- Allantoic pouches
- **Yolk sac remnant**
- Hippomane
- Fetal autolysis

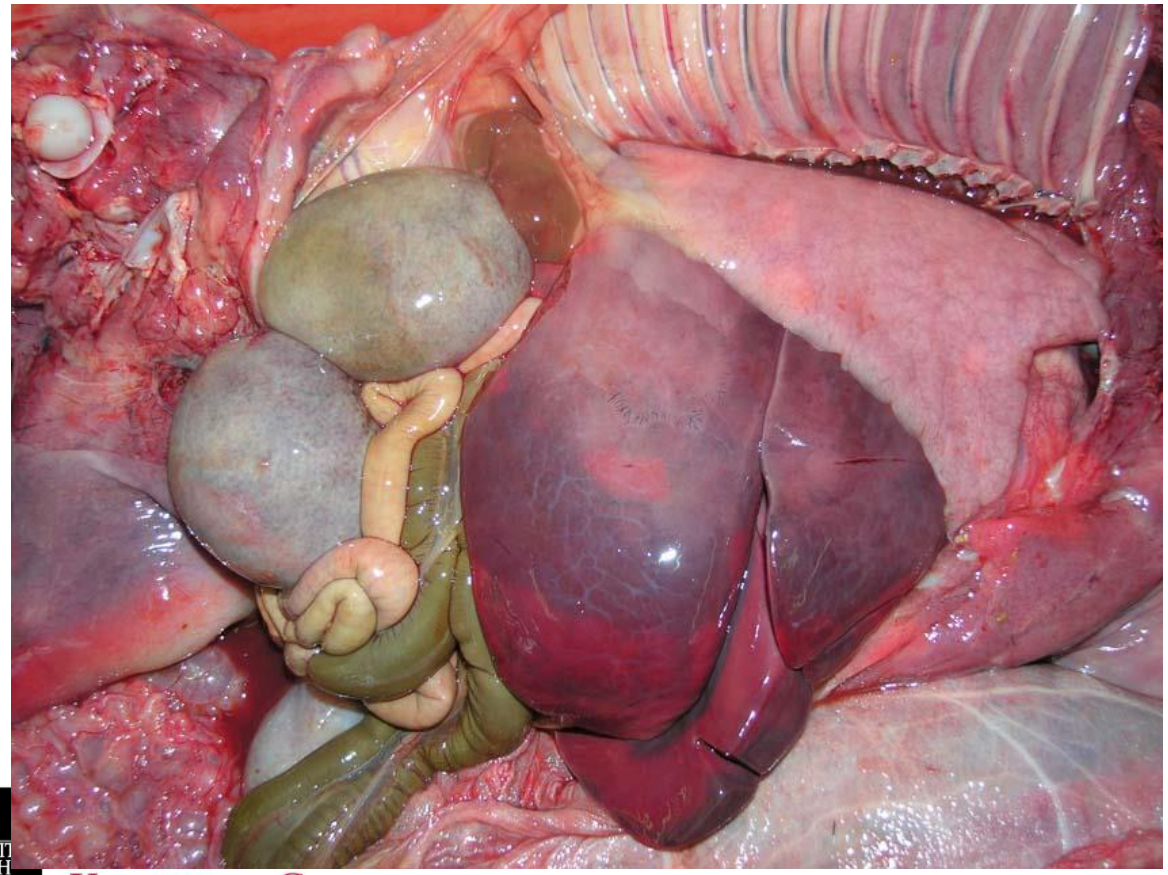


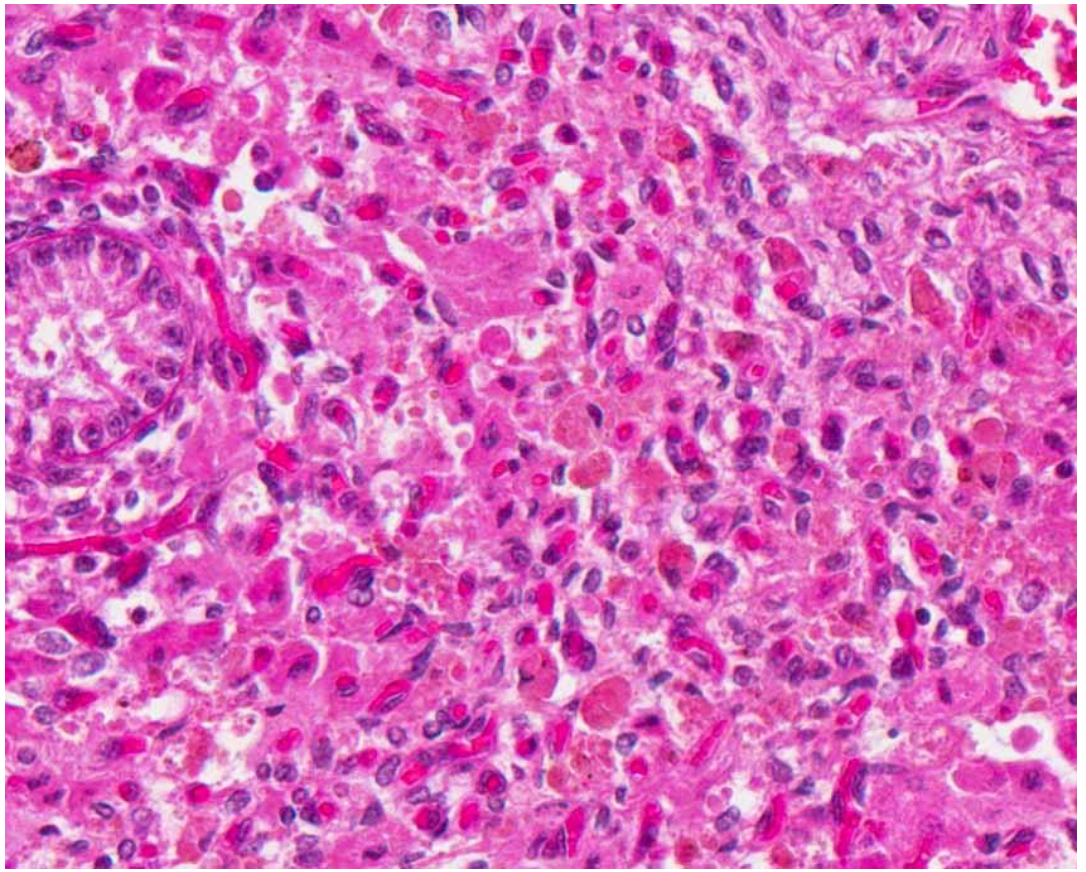
Nonlesion lesions

- Avillous regions
  - cervical star
  - chorioallantoic pouch
  - chorionic fold
- Allantoic pouches
- Yolk sac remnant
- **Hippomane**
- Gonadal hypertrophy
- Fetal autolysis



Gonadal hypertrophy





Know common diseases in your area

- No diagnosis 16%
- Noninfectious 47%
  - Foal
    - dystocia/trauma 19
    - congenital defects 10
  - Placenta
    - placental edema 7
    - twins 6
    - cord abnormality 3
    - body pregnancy 2
- Infectious 37%
  - Bacteria 18
  - Placentitis 10
  - EHV 4
  - Leptospirosis 2
  - Fungal 2
  - Nocardia 1

- Giles *et at*, Causes of abortion, stillbirth and perinatal death in horses. 3,527 cases. JAVMA 1993; 203: 1170-1175

Infectious causes of FOP

These are the classics!

Testing done at OVC on Equine study of *Neospora* Abortion

- Bacteria (culture/PCR)
  - Aerobic bacteria
  - *Leptospira interrogans* (Leptospirosis)
  - *Borrelia burgdorferi* (Lyme disease)
  - *Neorickettsia risticii* (Potomic horse fever)
  - *Anaplasma phagocytophilum* (Equine granulocytic anaplasmosis)
- Protozoa
  - *Neospora caninum* (object of study)
  - *Neospora hughesi*
- Virus
  - *Equid alphaherpesvirus 1* (Equine herpesvirus 1)
  - *Equid alphaarterivirus* (Equine arteritis virus [EAV])

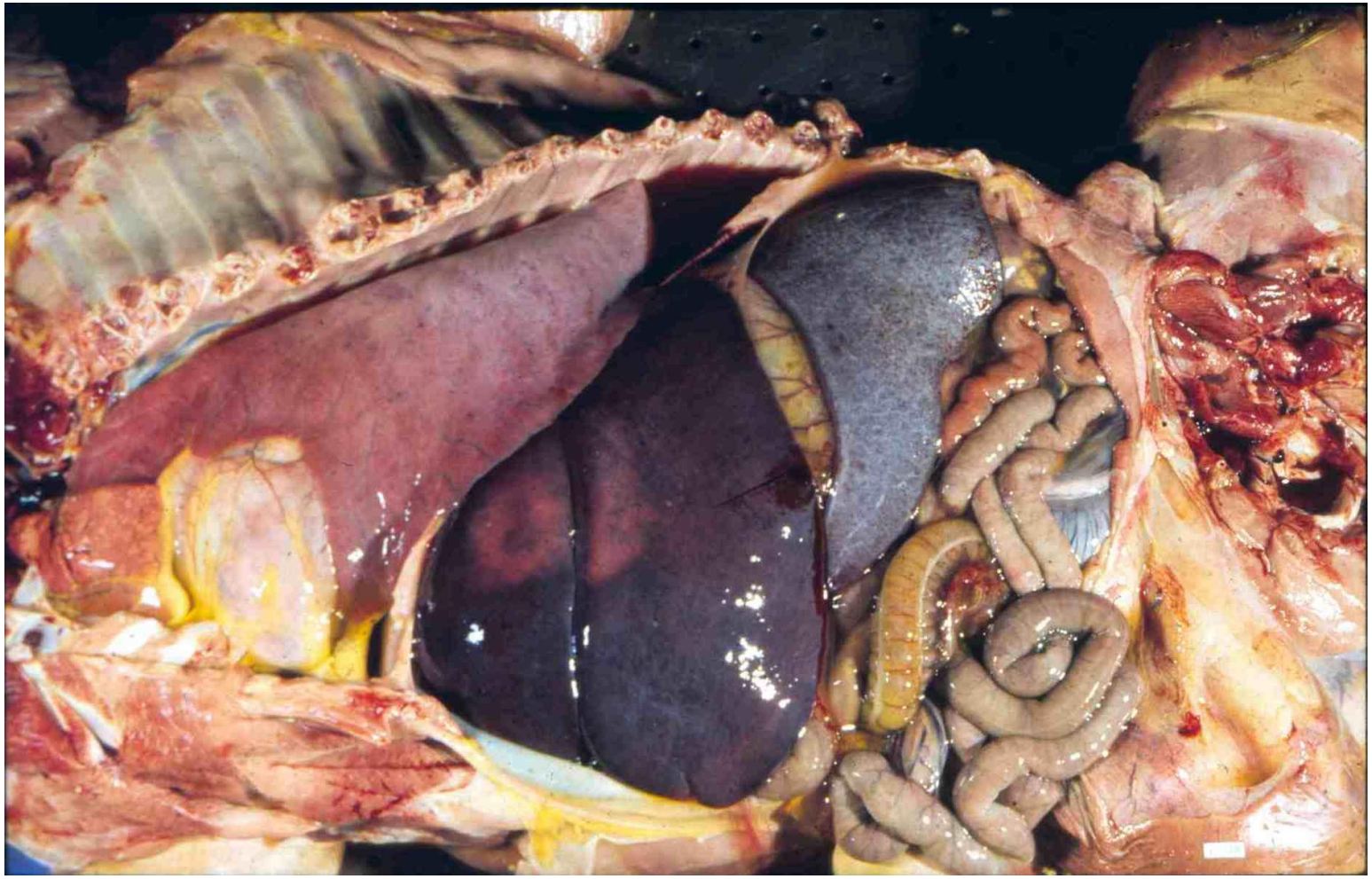
Olivia Johns, Tracey Chenier, David Pearl, Robert Foster

University of Guelph
Ontario Veterinary College
Department of Pathobiology

Equid alphaherpesvirus 1

Interstitial pneumonia

Focal hepatic necrosis



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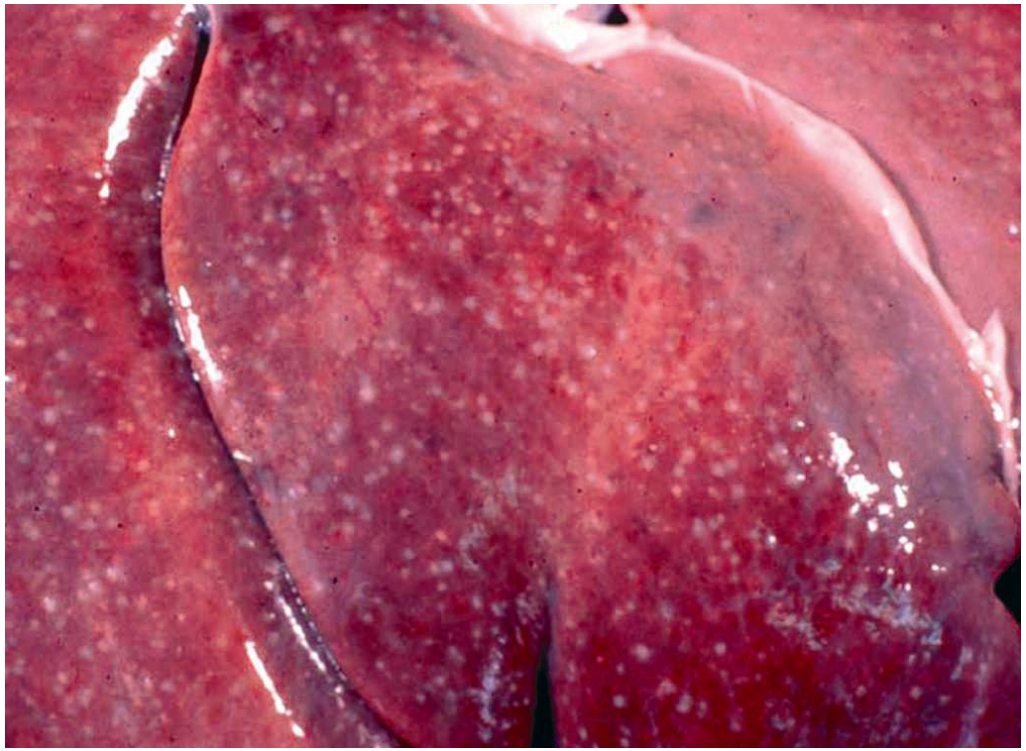
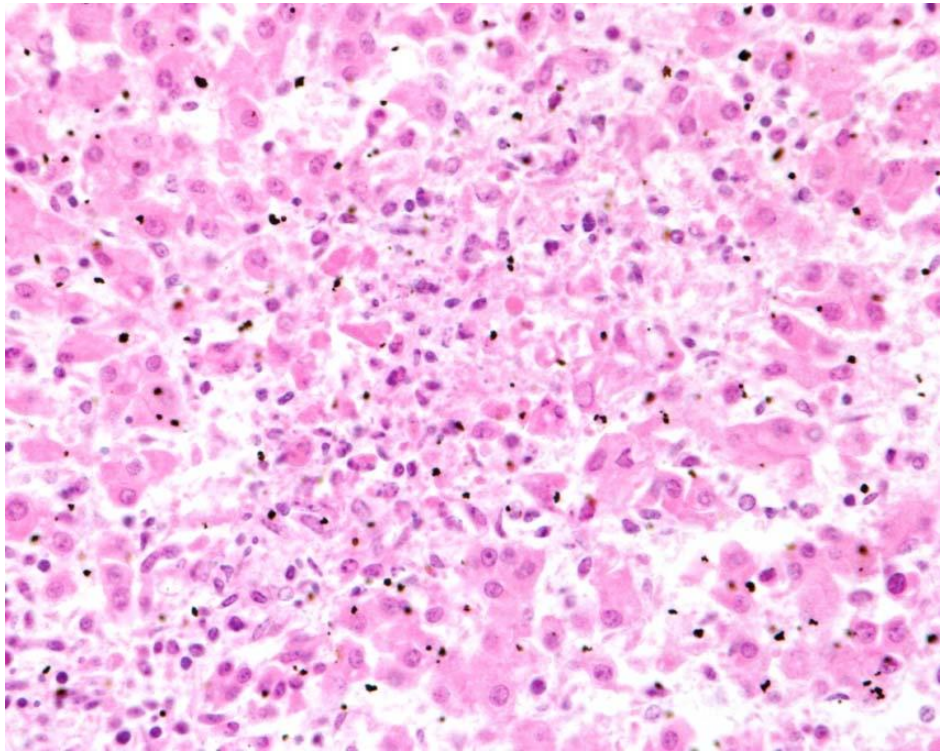
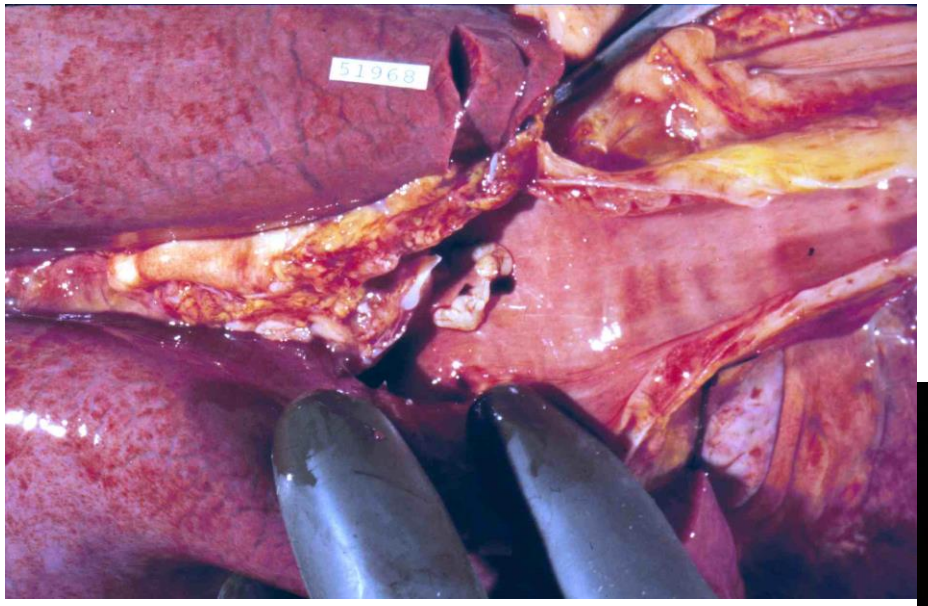
Equid alphaherpesvirus 1 (EHV-1)



Focal hepatic necrosis



Equid alphaherpesvirus 1

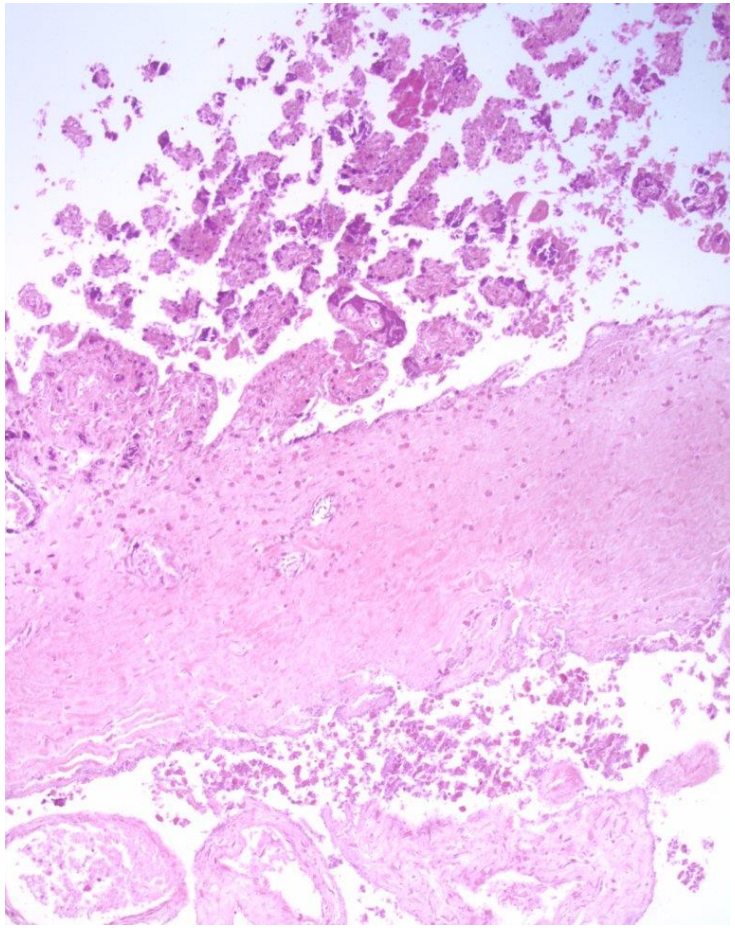


Fibrin cast in trachea

Placentitis

- Ascending infection
  - *Streptococcus equi zooepidemicus*
- Nocardioform actinomycetes
  - Body of placenta!
- Equine amnionitis and fetal loss (see later)

Ascending infection
Streptococcus equi zooepidemicus



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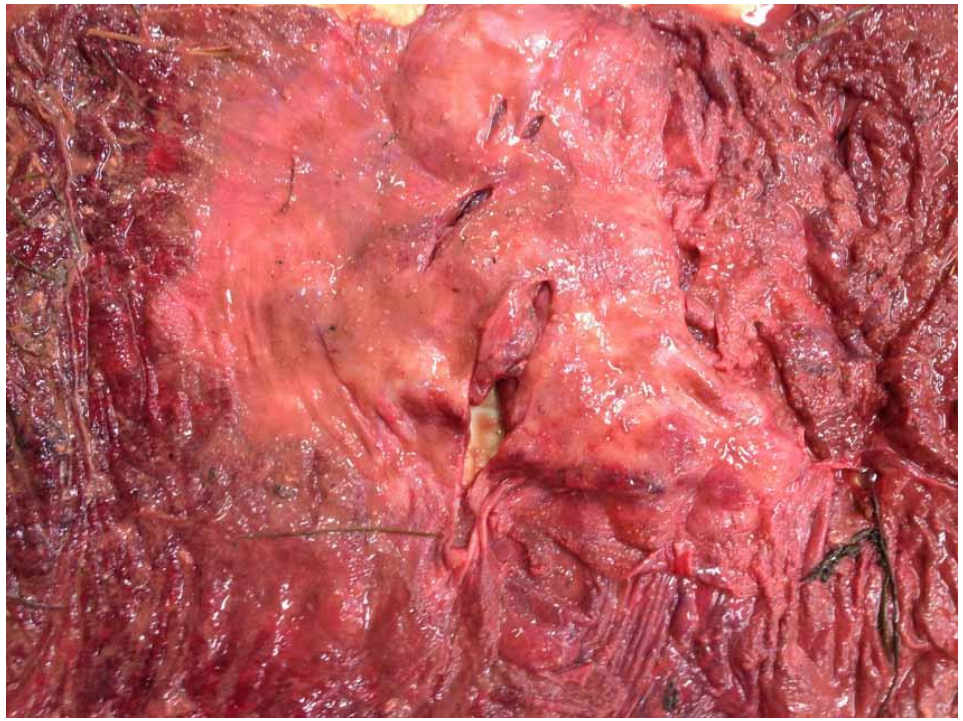
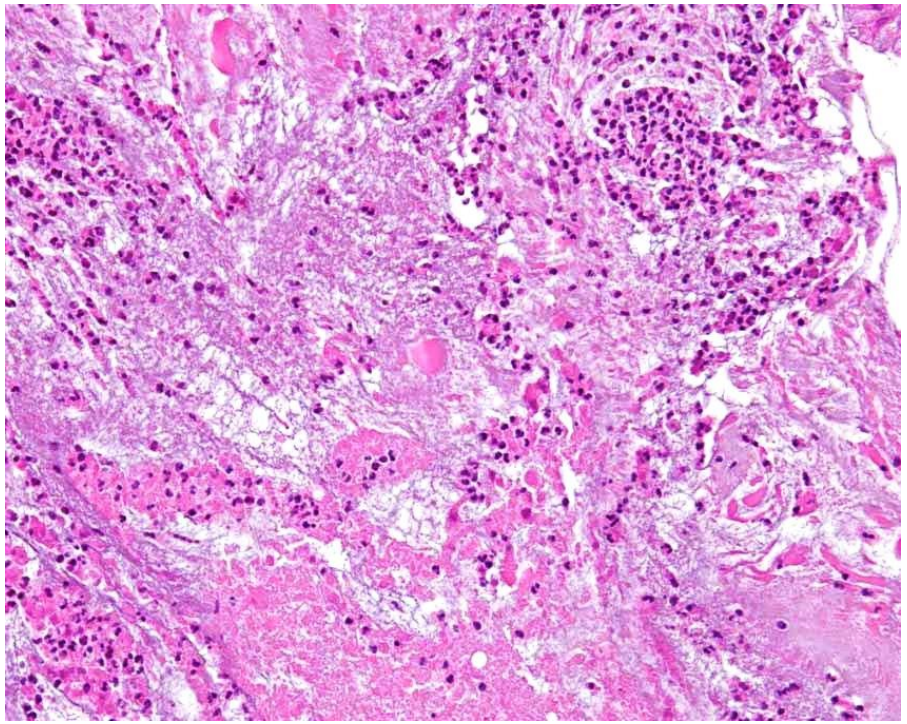
Photograph complements of
Dr Tracey Chenier

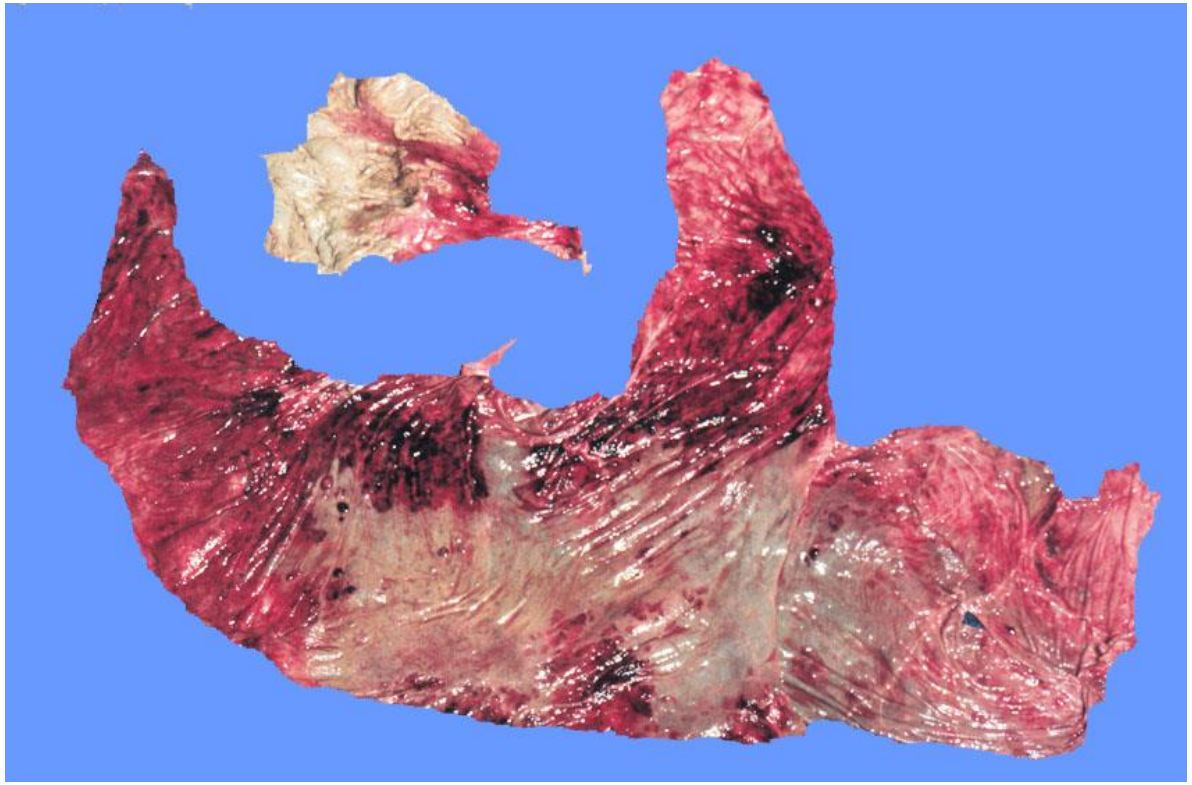
Horse: Nocardioform Placentitis

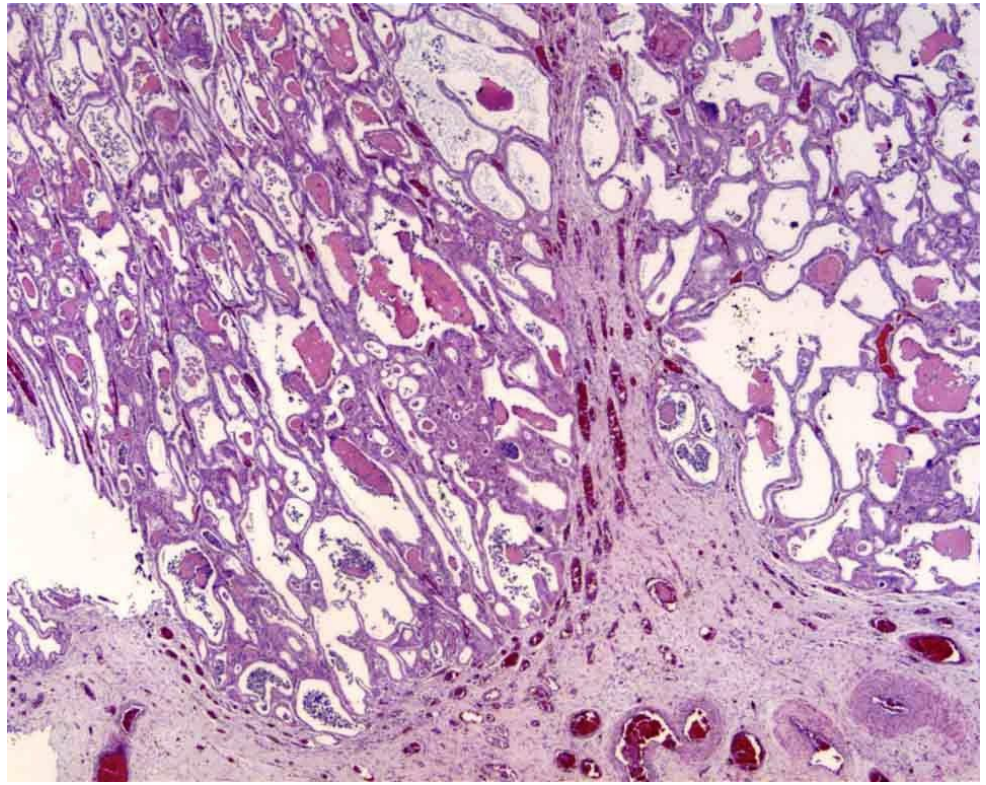
- Body of placenta - Brown viscus exudate





Horse: Allantoic dysplasia





Noninfectious Equine FOP

Fetus and Placenta including cord
Maternal
Fetal Maternal incompatability
Paternal

"do what you can, and can the rest"

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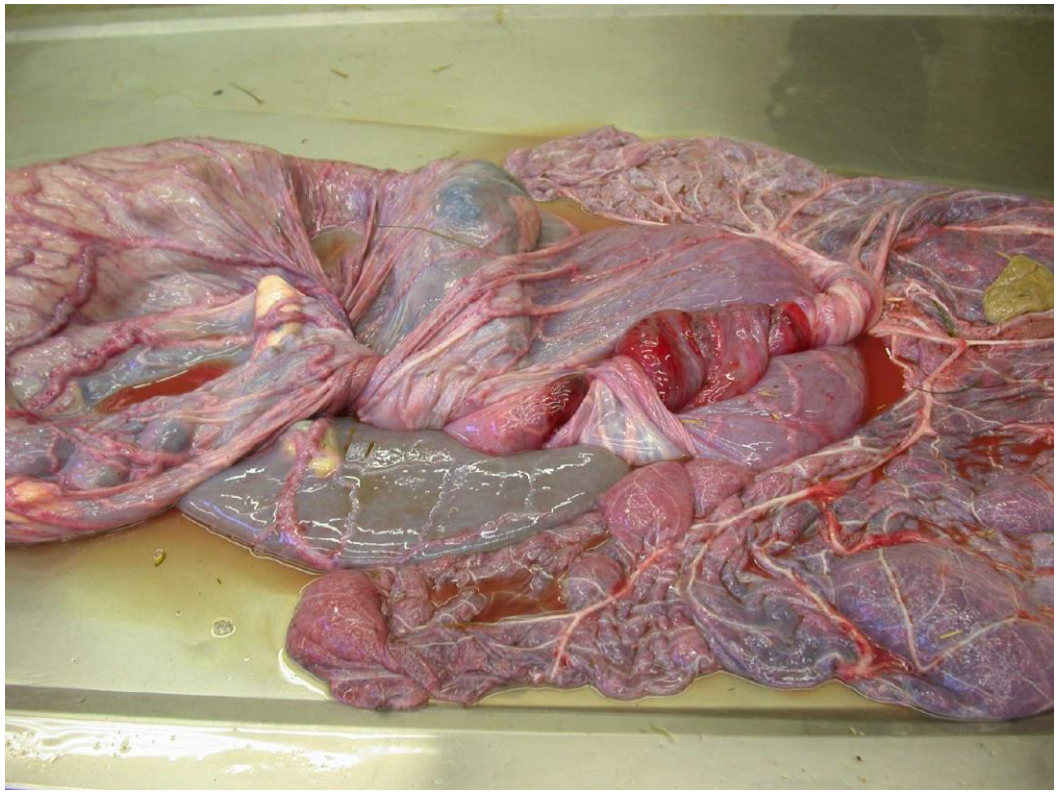
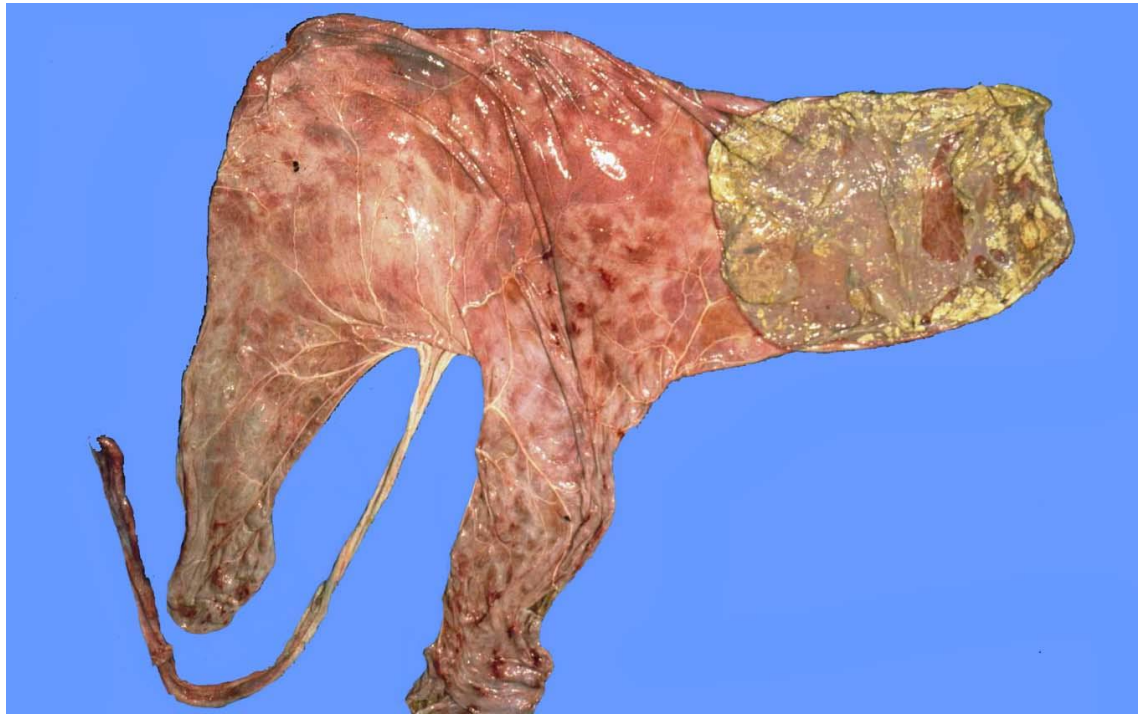
Cord Abnormalities

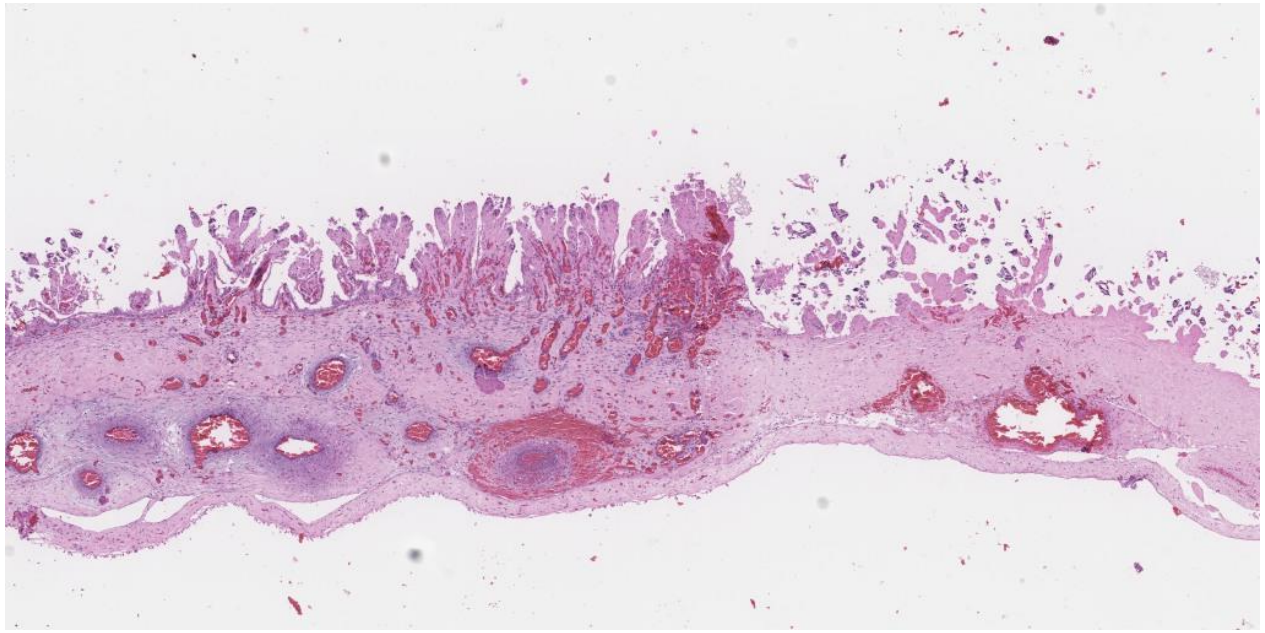
- too short <36 cm
- too long >83 cm
  - placental infarct
  - excessive torsion
  - Strangulation
- One umbilical artery

Cord abnormalities – excessive torsion



Placental infarct





Reduced placental reserve

- Avillus regions
  - **twinning**
  - premature separation
  - body pregnancy
  - reduced histotrophic and hemotrophic function

Twinning

Reduced placental reserve

- Avillus regions
  - twinning
  - **premature separation**
    - **Red bag delivery**
  - body pregnancy
  - reduced histotrophic and hemotrophic function

Photo complements of Dr. Tracey Chenier

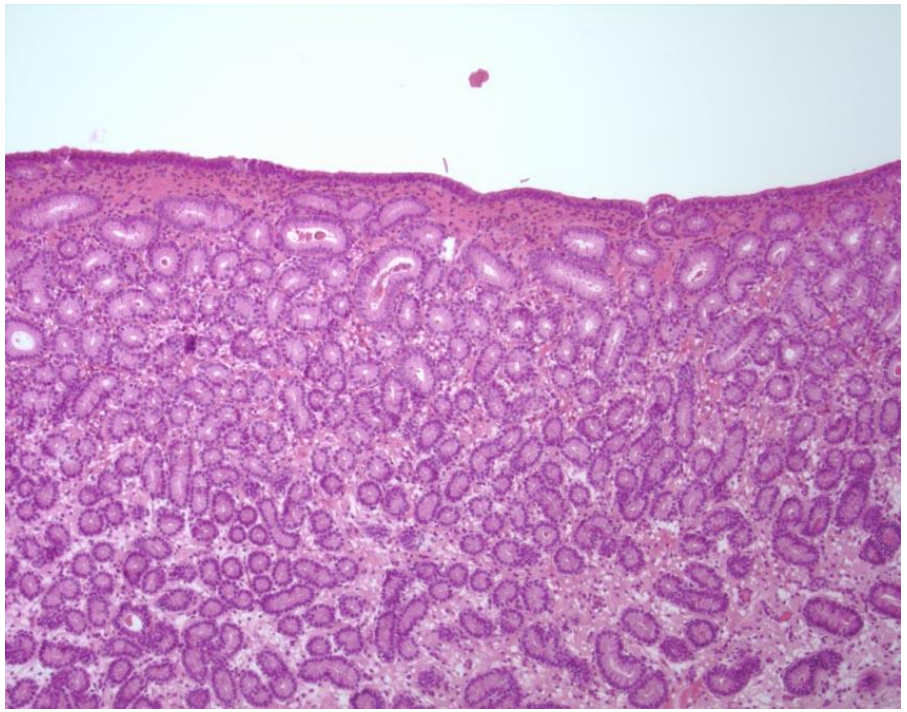
Reduced placental reserve

- twins
- premature separation
- **body pregnancy**
- reduced histotrophic and hemotrophic function

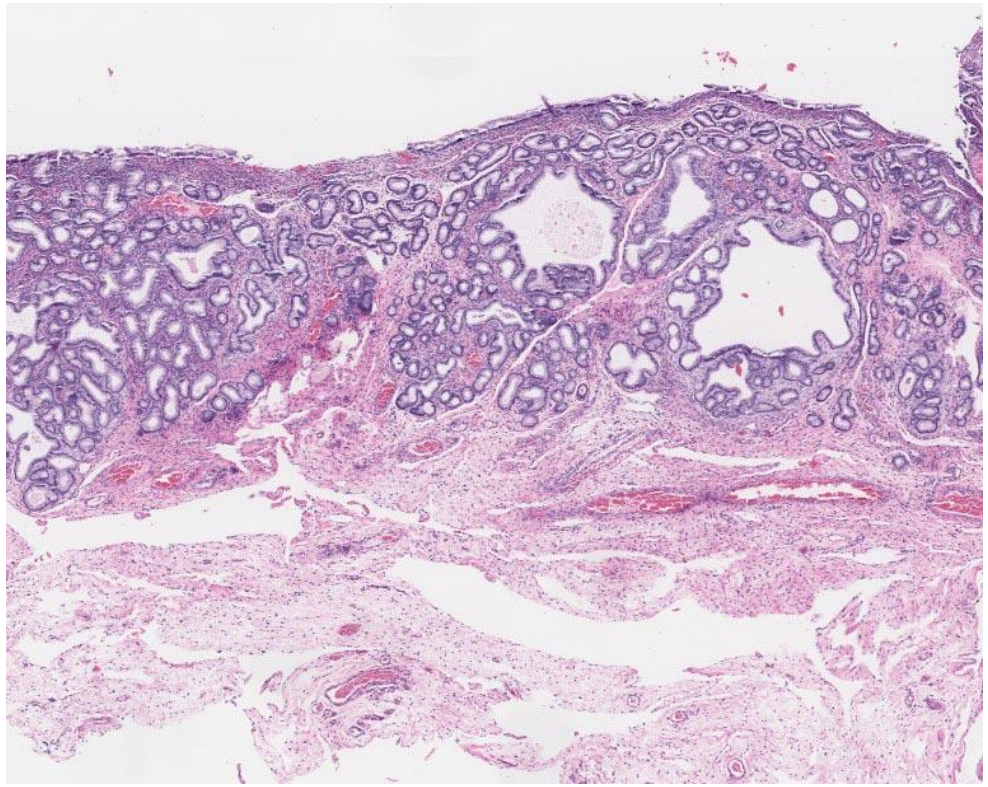
Reduced placental reserve

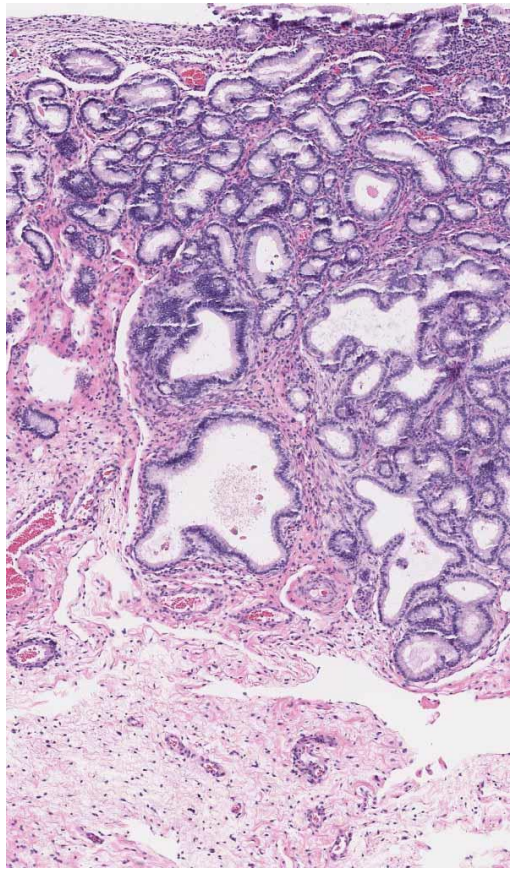
- Twins
- premature separation
- body pregnancy
- **reduced histotrophic and hemotrophic function**
  - **endometrial fibrosis and altered glands**
  - **endometrial biopsy**

Endometrial fibrosis

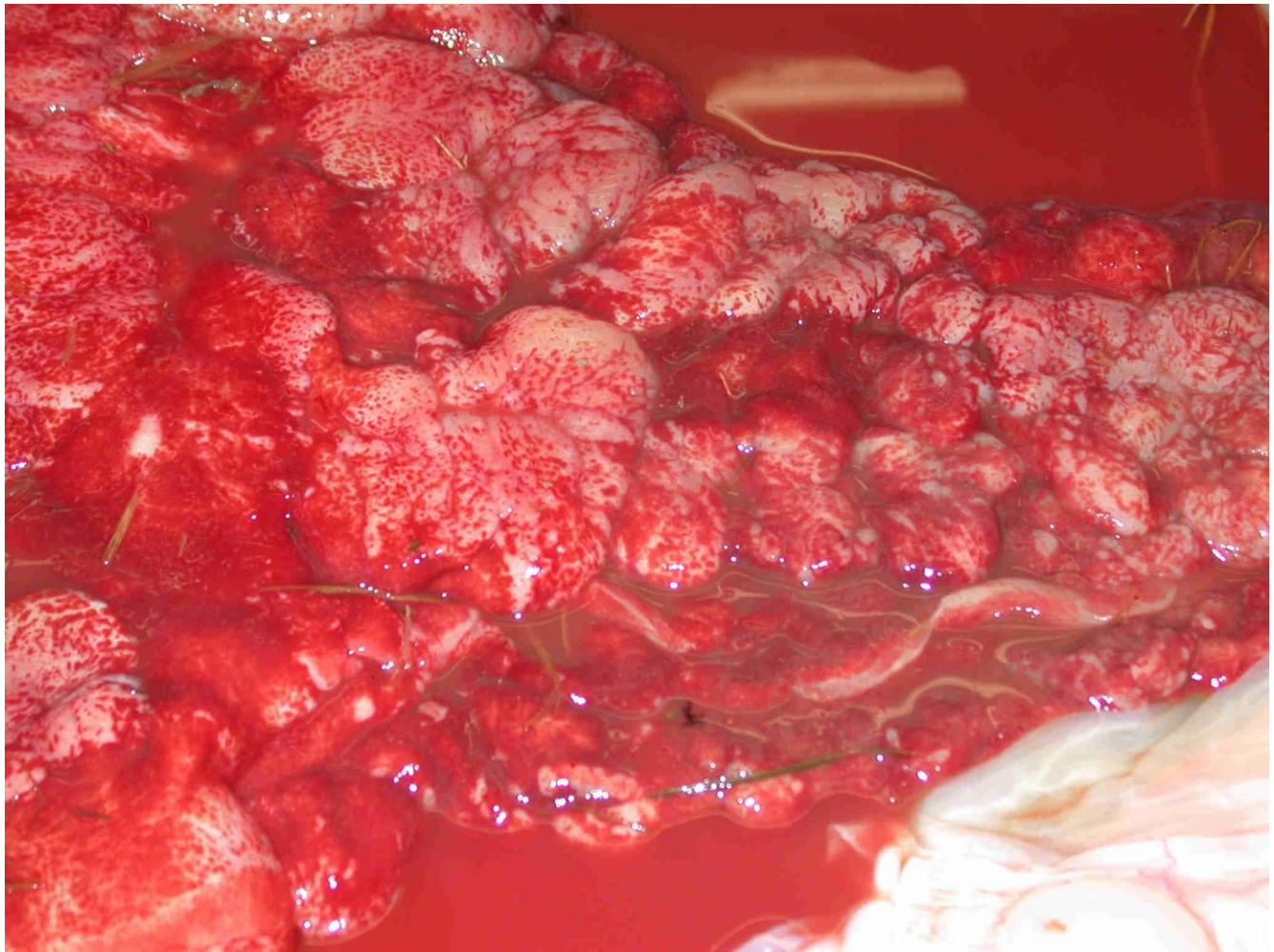


Normal endometrium





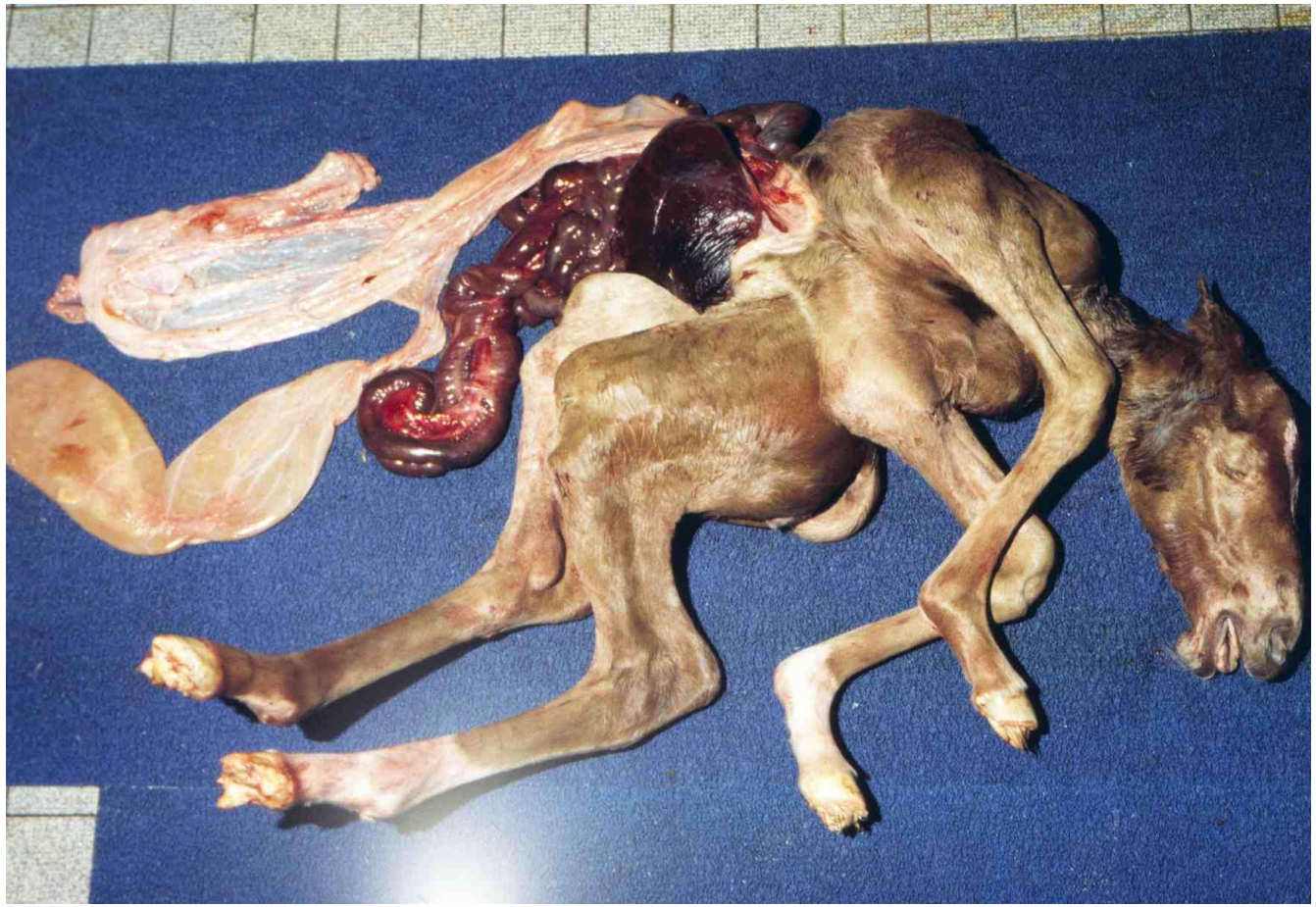
Placental Edema: Endophyte toxicosis



Placental edema

- **Endophyte mycotoxicosis**
  - *Neotyphodium sp. (loli, coenophialum)*
  - *Claviceps purpurea*
  - Ergot (ergopeptine) alkaloids (vasoactive and prolactin)
  - Hyperthermia
  - Placental edema and thickening
  - Hypothyroidism and Dysmaturity
  - Prolonged gestation

Horse: Congenital abnormalities



Schistosomus reflexus

Schism – division
Soma – body

Fetal lesions

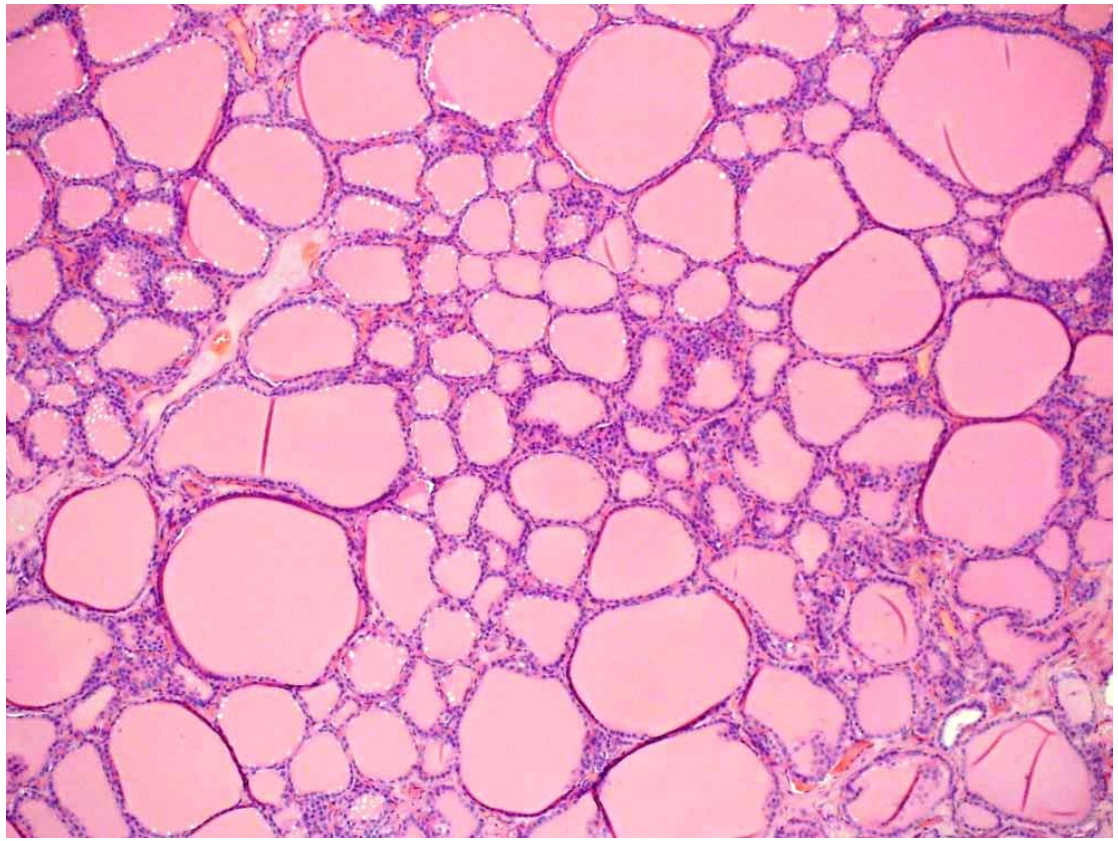
- Fetus
  - Dystocia
  - Congenital anomalies
  - Genetic disorders
  - **Nutritional**
    - **Musculoskeletal disease and Thyroid hyperplasia**

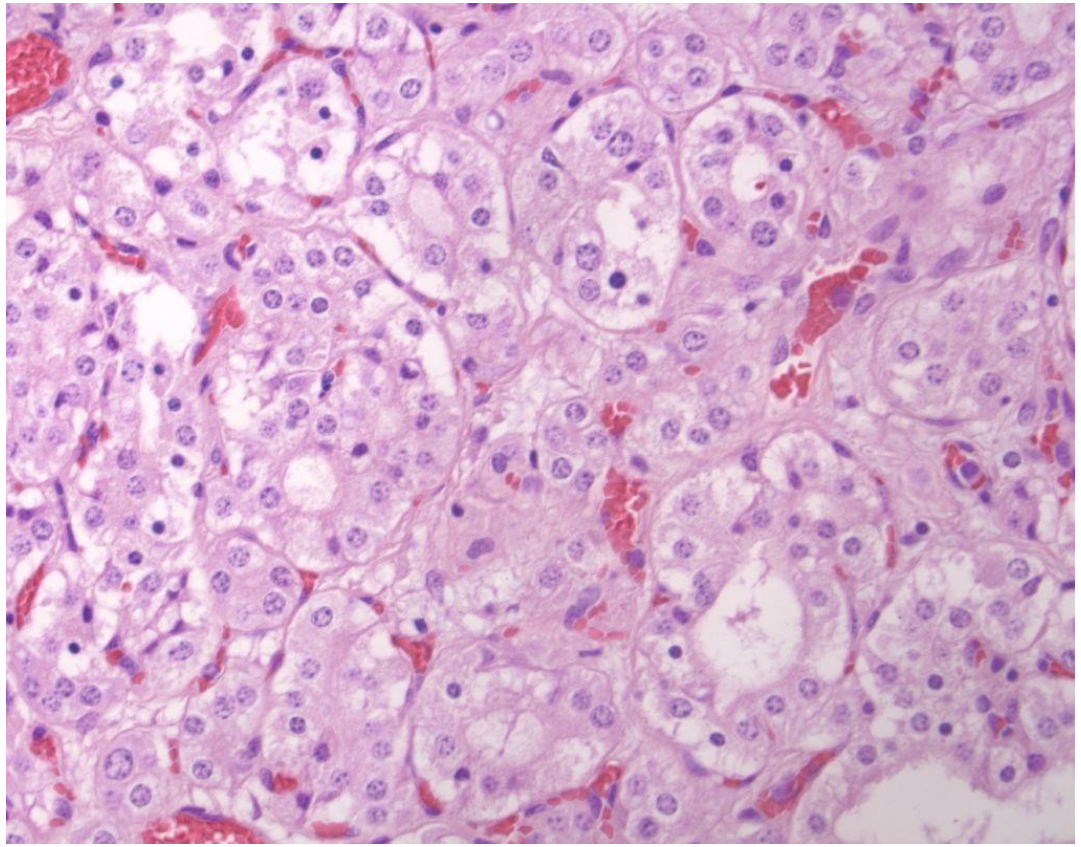
Musculoskeletal disease and thyroid hyperplasia

- Variety of skeletal abnormalities
  - Limb deformities
  - Arthrogryposis
  - Osteopetrosis
- Microscopic thyroid hyperplasia
- Poor feeds - nitrite/nitrate

Arthros – joint, gryposis – abnormal curvature, Osteo – bone, petros - rock

THMSD – thyroid histology





Normal

Bovine Failure of Pregnancy

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Causes of Bovine Abortion

No diagnosis	**58**
Noninfectious	**1**
Infectious	**42**
Bacterial	17
Protozoal	16
Viral	4
Fungal	4
Ureaplasma	2

Disease of the Bovine Fetus

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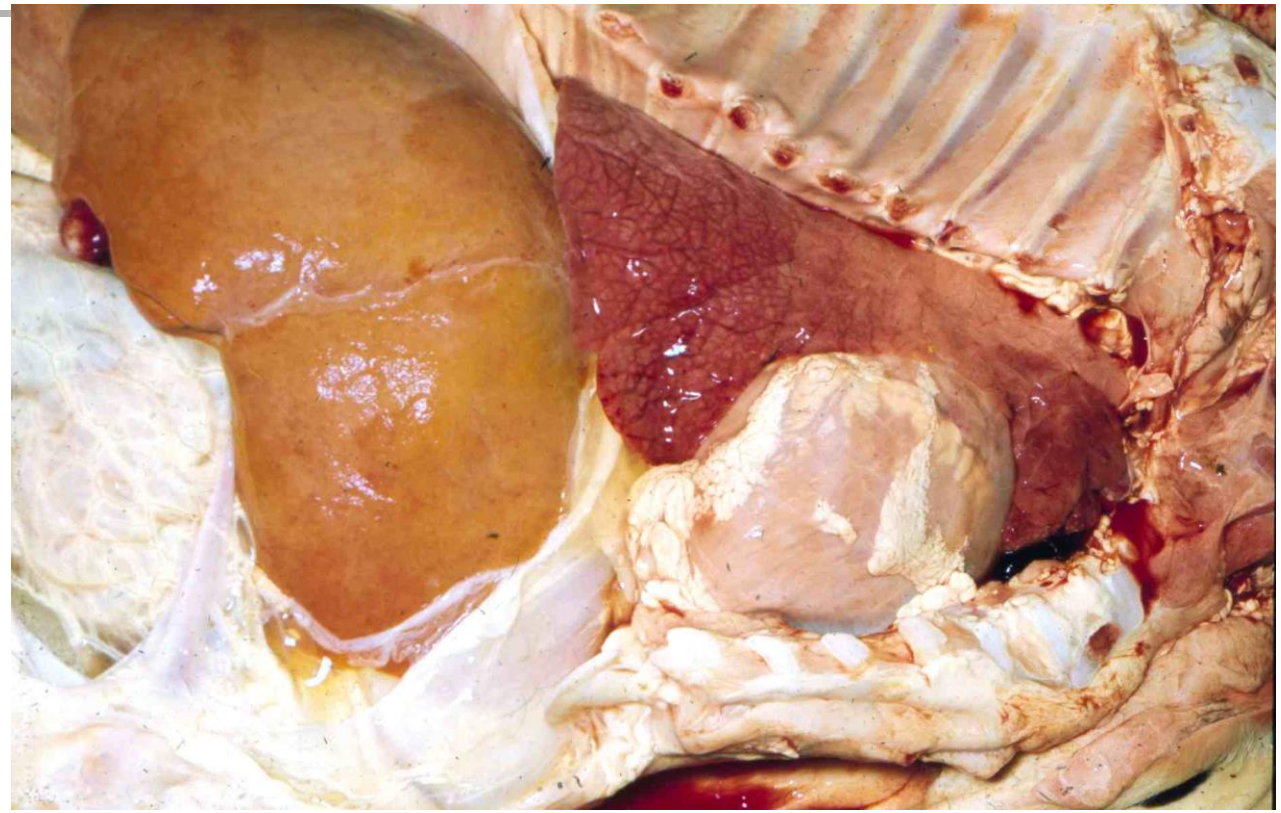
Fetal lesions

- Dermatitis
  - Mycotic
- Heart failure
- Focal necrosis in liver

Fetal lesions

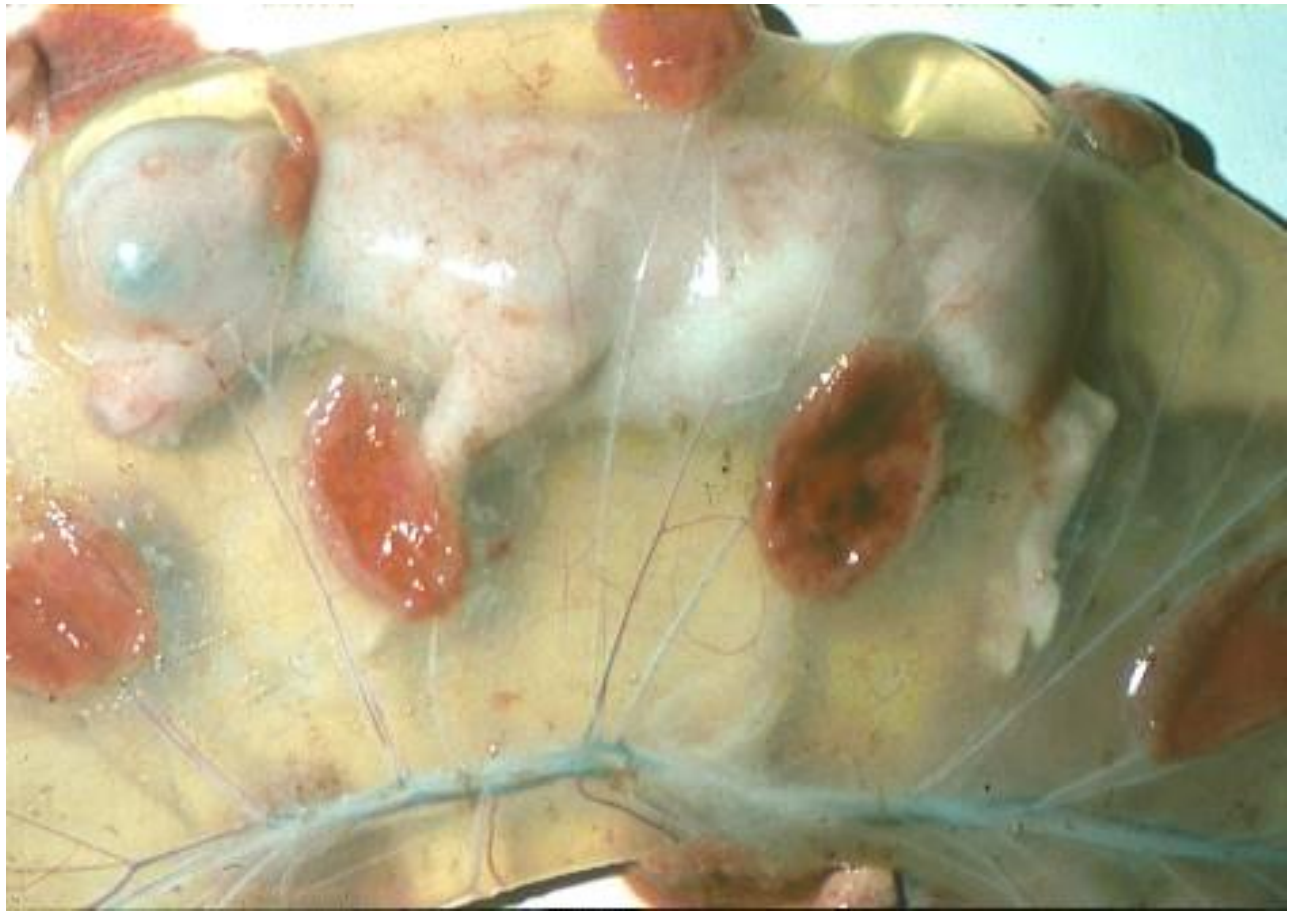
- Dermatitis
  - mycotic
- Heart failure
  - *Pestivirus A, B* (BVDV)
  - *Neospora caninum*
  - Vit E / Selenium
- Focal necrosis in liver



Photograph compliments of
Dr Richard Miller

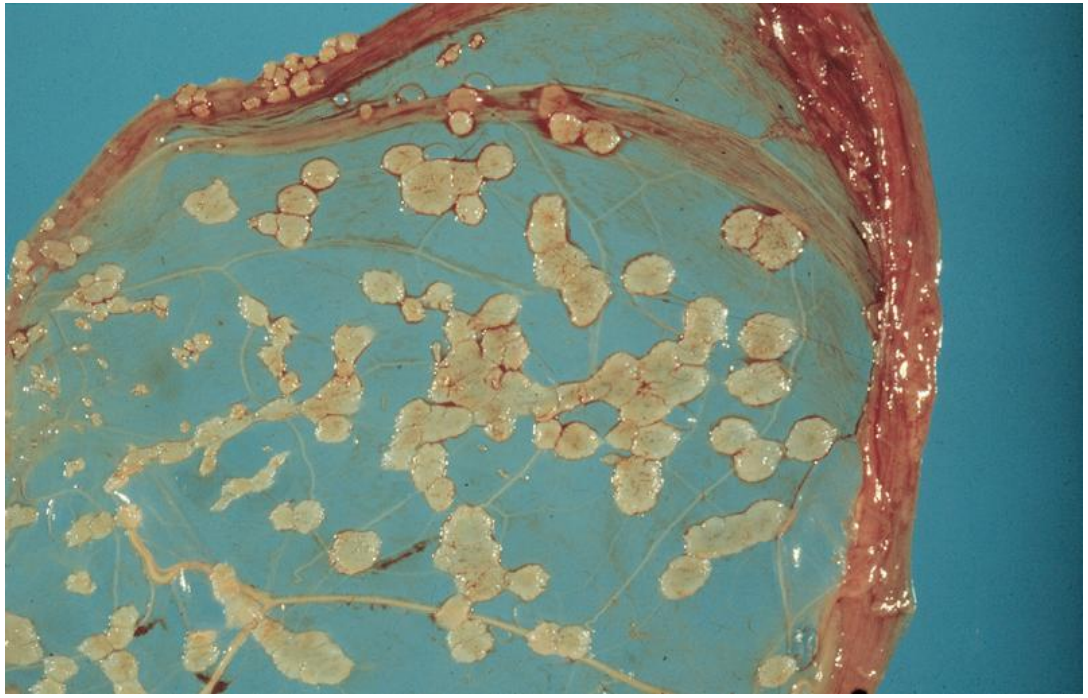
Normal uterus

Normal Chorionic surface

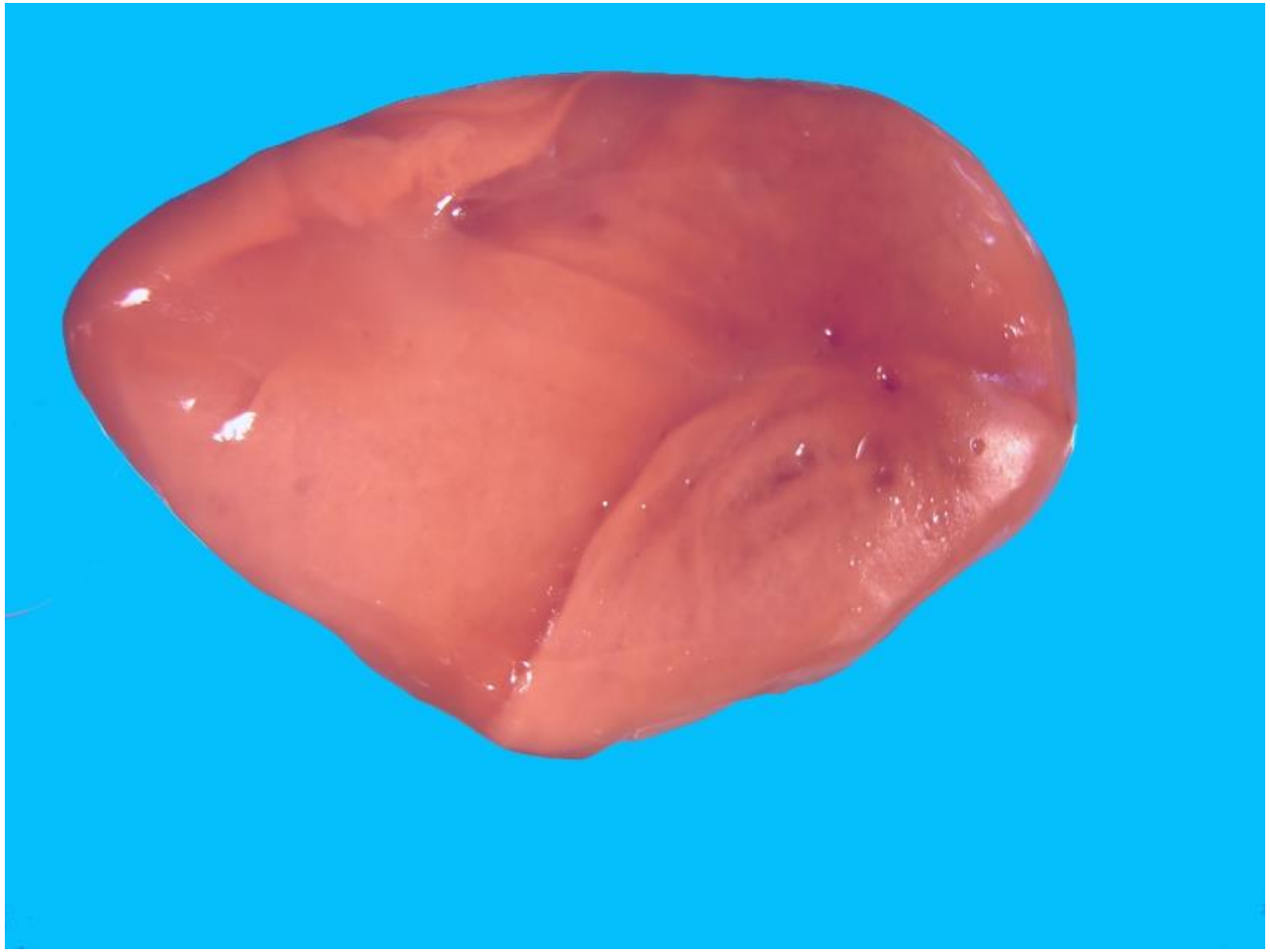


Placental mineralization

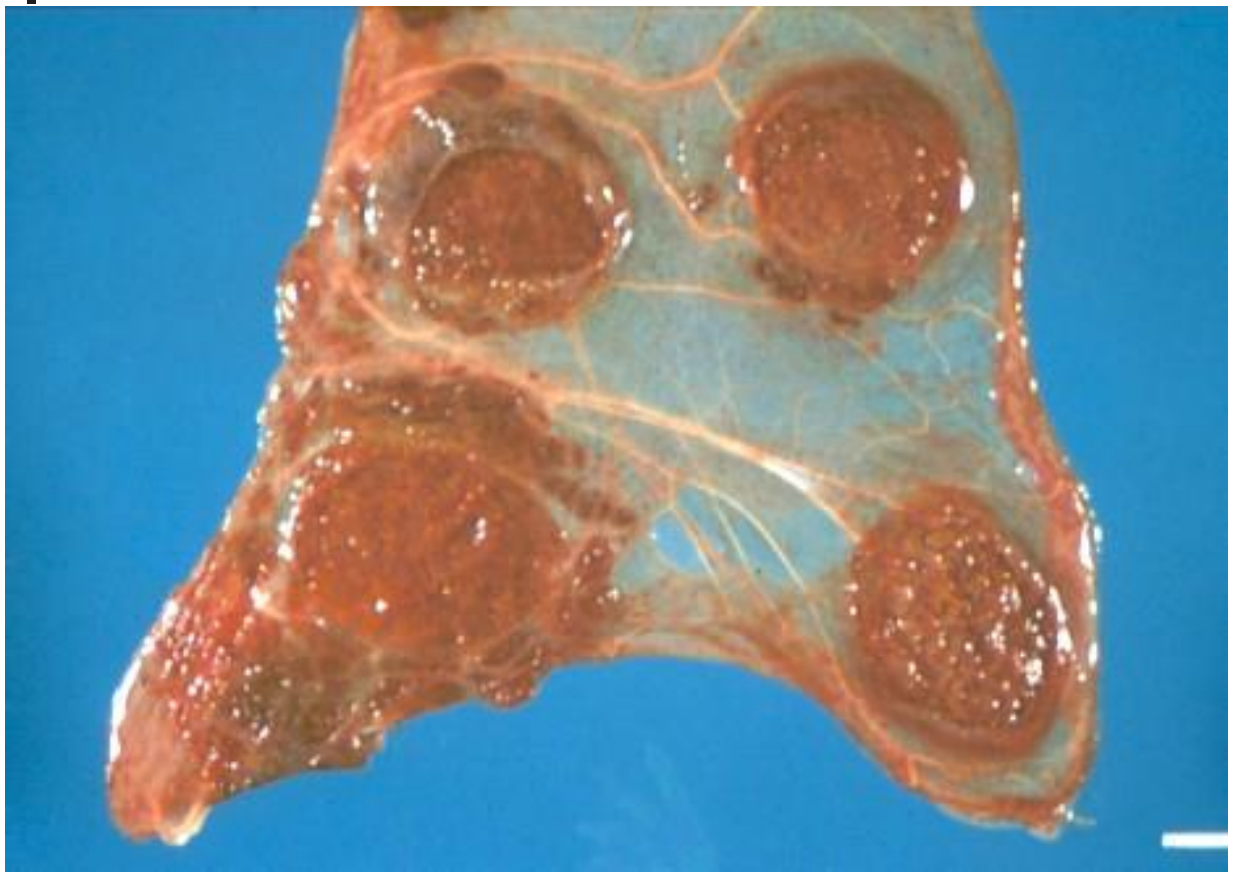
Amniotic plaques are normal



Hippomane



Bovine: Adventitial placentation



placenta

Endometrium

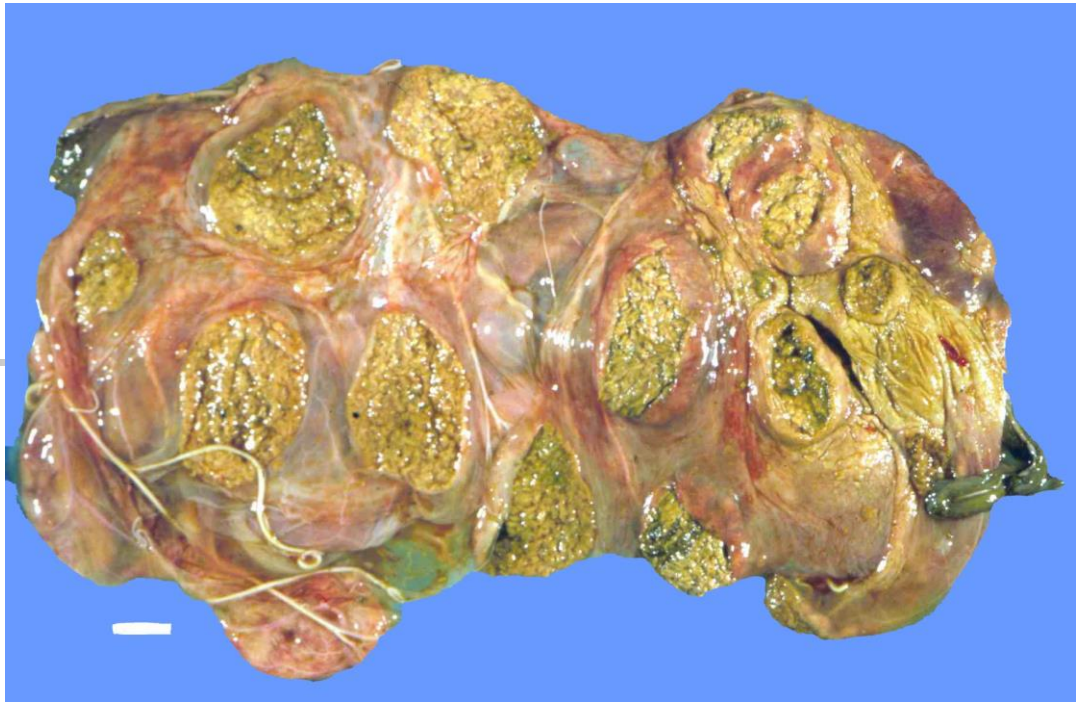
Amorphous globosis

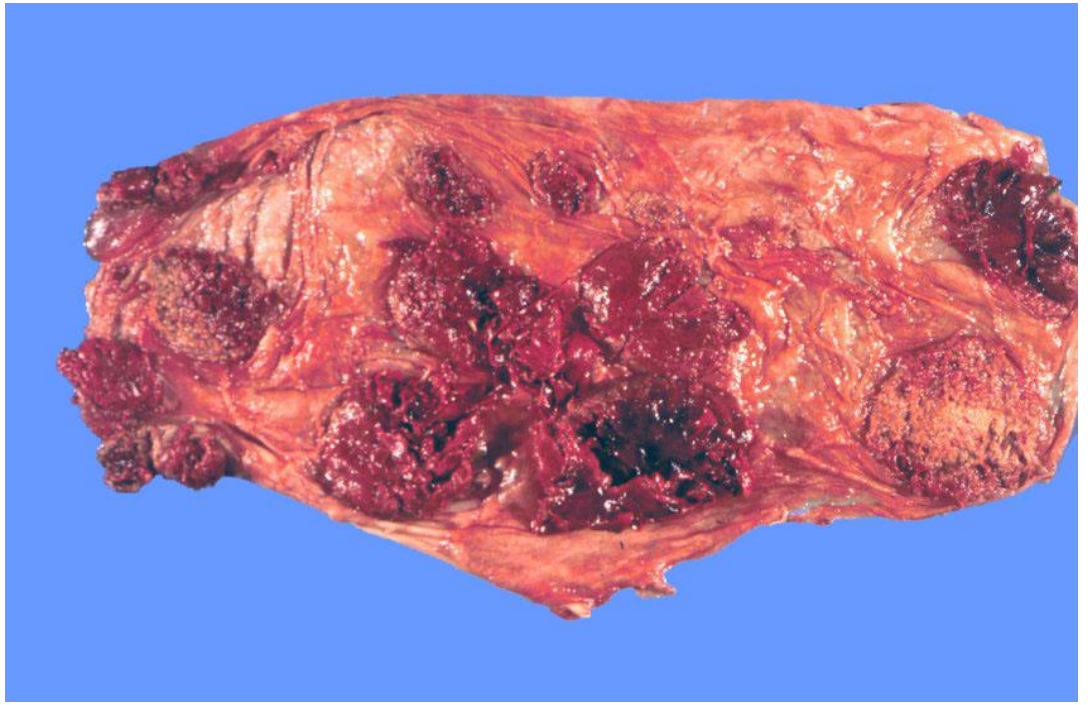
- Remains of a cotwin.
- Not a yolk sac remnant

Placentitis

- edema
- exudate
- necrosis of cotyledon
- thickening of intercotyledonary placenta
- cupping of cotyledon

- Bacterial
- Fungal





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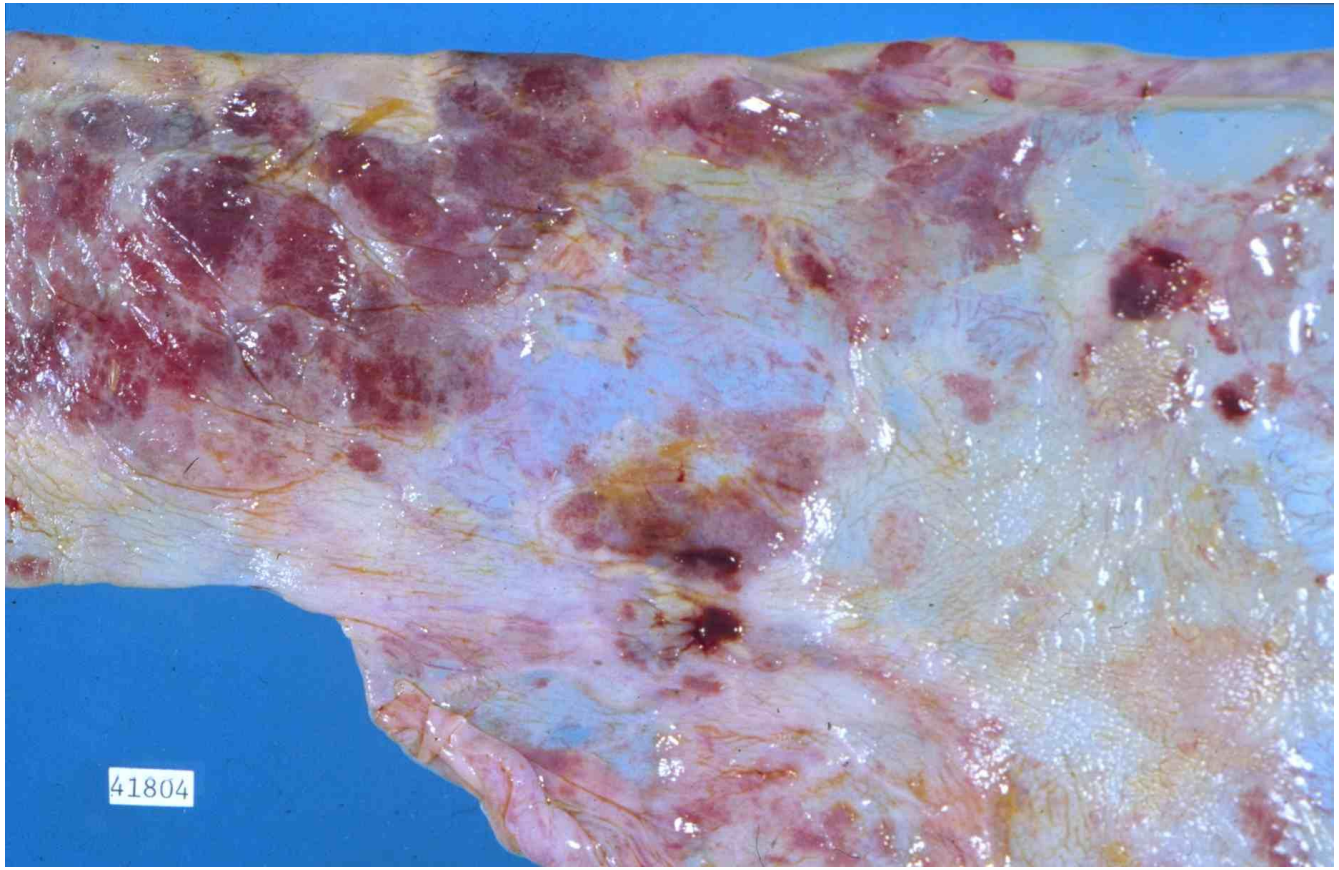
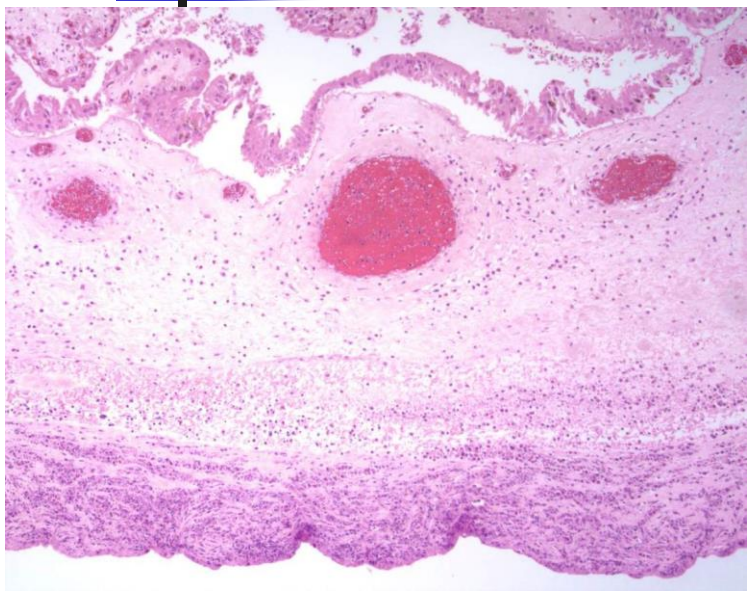
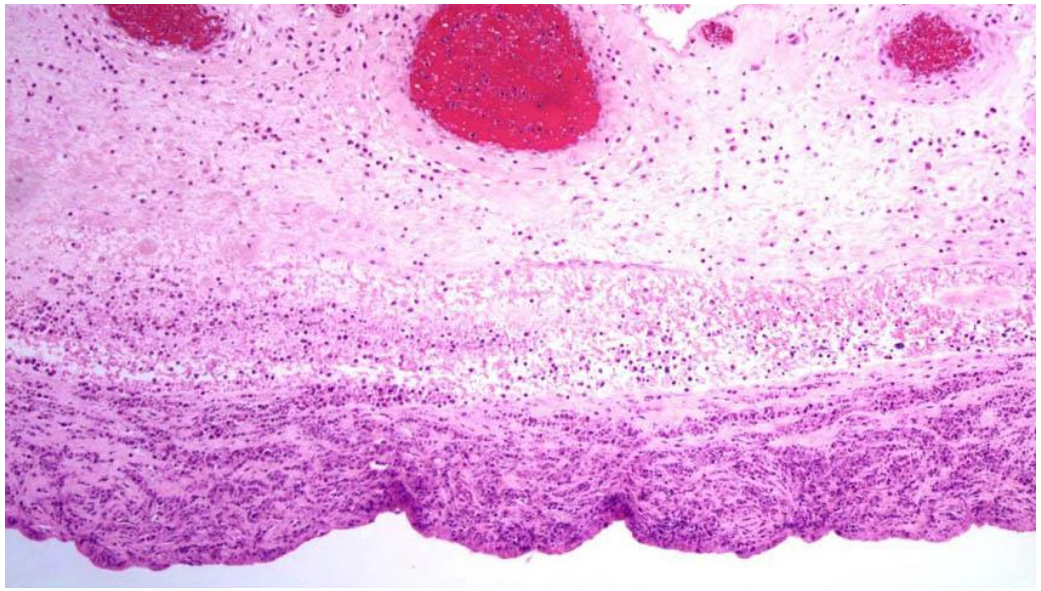
Amnionitis

- Ureaplasma
- Rarely
  - mycotic
  - bacterial

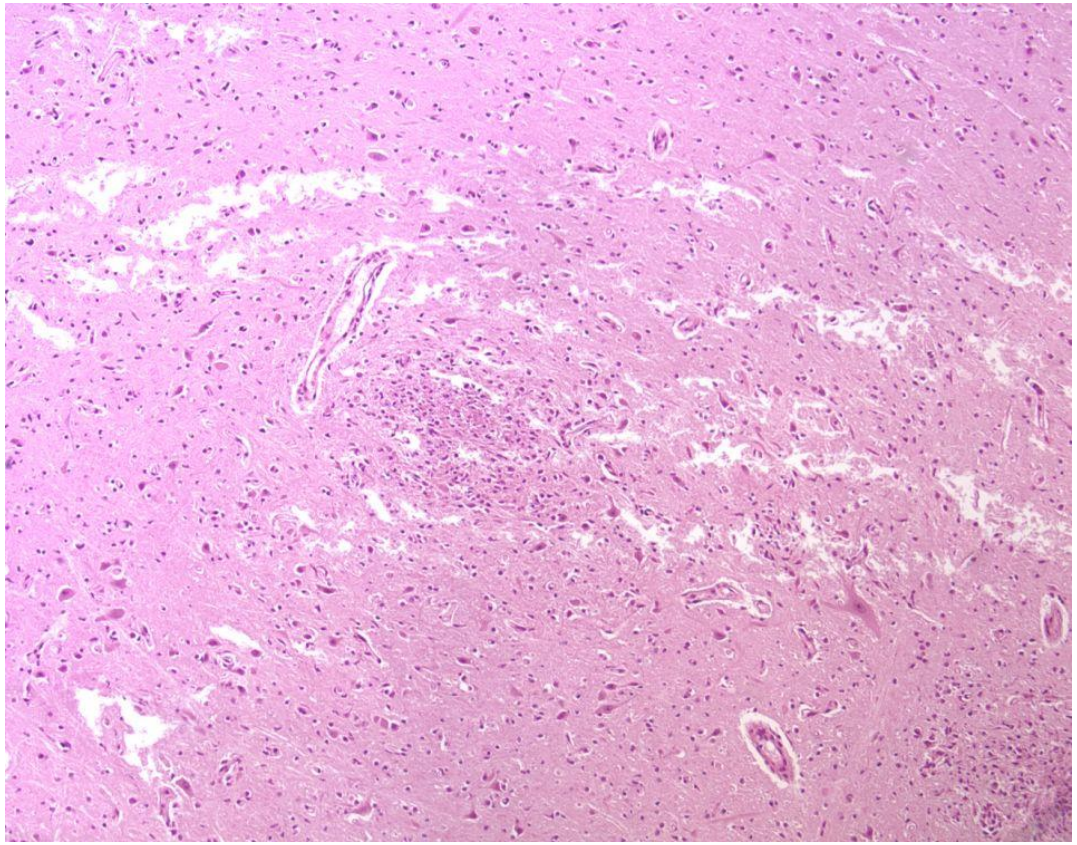


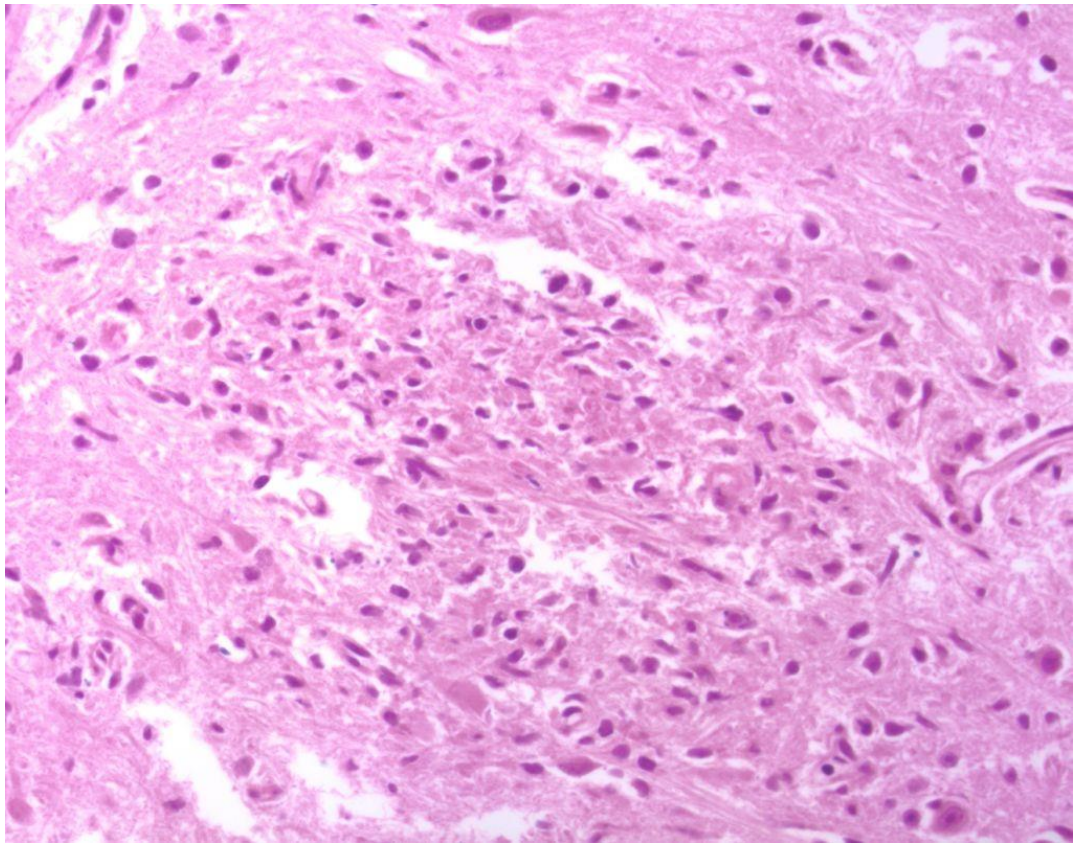
Ureaplasma diversum





Neospora caninum





Ovine and Caprine Failure of Pregnancy

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Small Ruminant

- Infectious causes are more common in the list of diagnoses
- CCC and T: *Chlamydia, Coxiella*, *Campylobacter* and *Toxoplasma*
- *Chlamydia* and *Coxiella* are zoonotic.

Ovine Abortion*

- No Diagnosis 48
- Noninfectious 2
- Infectious 50
  - *Chlamydia abortus* 17
  - *Campylobacter* 4
  - *Toxoplasma gondii* 19
  - *Coxiella burnetii* 5
  - Virus 0

* Animal Health Laboratory, University of Guelph

Goats

No diagnosis	52
Noninfectious	4
Infectious	40
▪ *Coxiella burnetii*	13
▪ *Chlamydia abortus*	9
▪ *Toxoplasma gondii*	9
▪ Bacteria	3

Disease of the Ovine and Caprine Fetus

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Cyclopia and holoprosencephaly

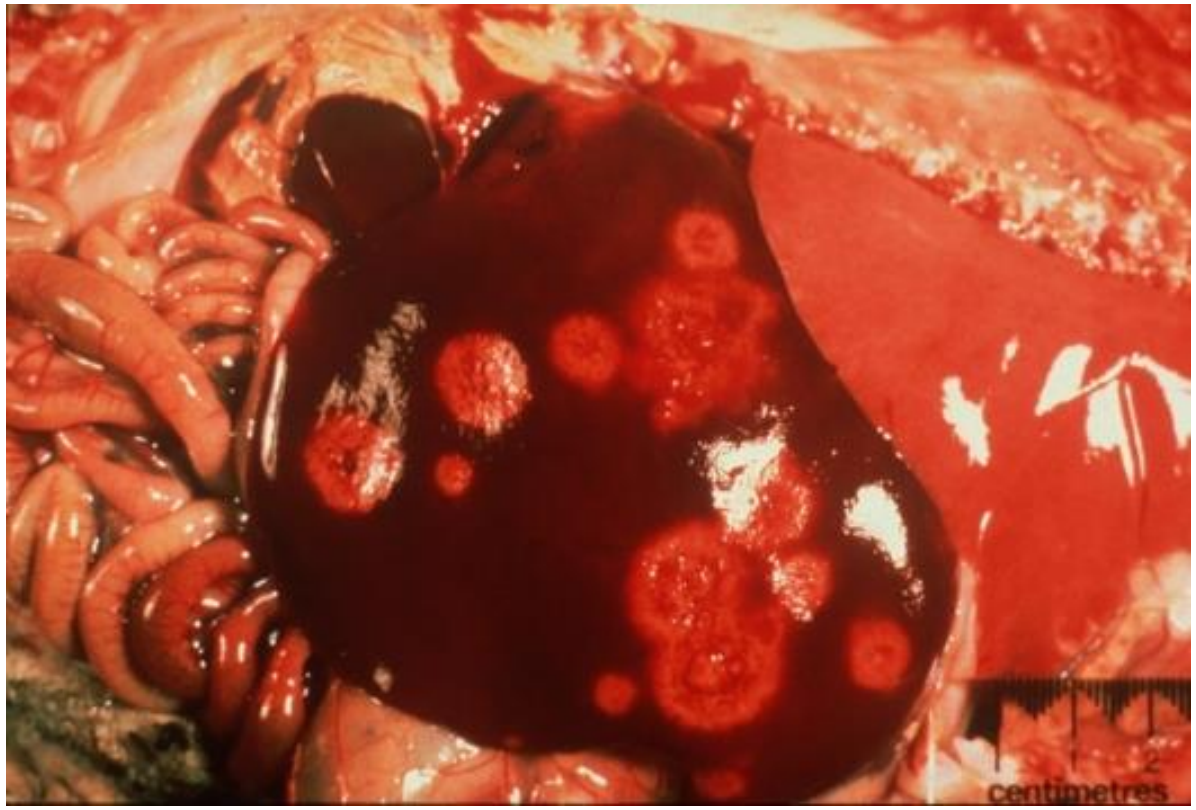
Cache Valley orthobunyavirus
Schmallenberg orthobunyavirus
Bluetongue virus

Hydranencephaly, arthrogryposis

- *Cache Valley orthobunyavirus*
- *Schmallenberg orthobunyavirus*
- *Bluetongue virus*

Fetal lesions

- Hepatic necrosis
  - Large multifocal
    - Campylobacter, C.jejuni, fetus fetus, and fetus venerealis.
    - Helicobacter sp
  - Small multifocal
    - Listeria monocytogenes

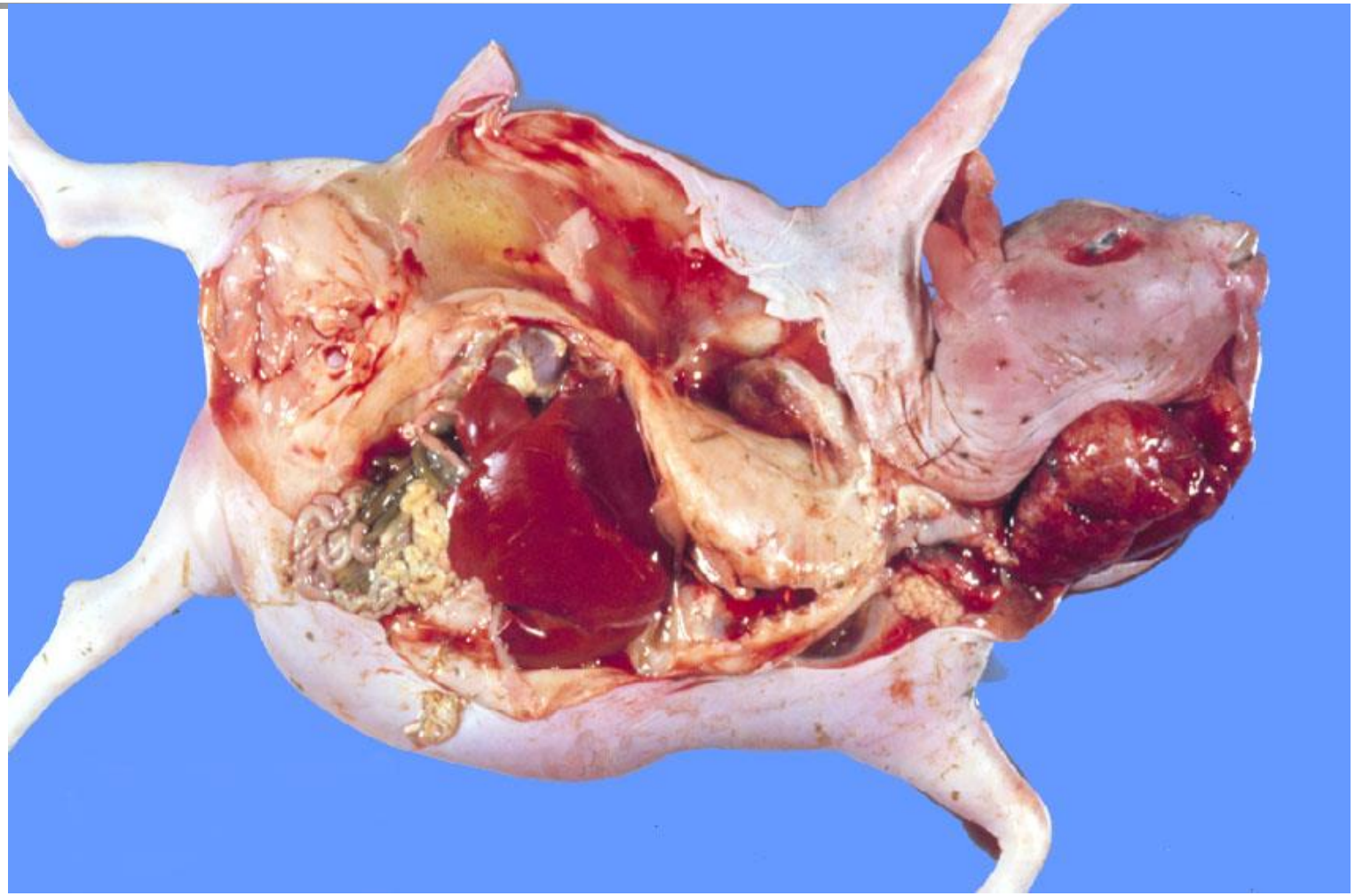


Photograph complements of
Dr Dennis Wilson

Congenital hypothyroidism - Iodine deficiency

- Goitre
- Alopecia
- Myxoedema

- Hypomyelination



Disease of Ovine and Caprine Placenta

Chronic placentitis (CCC)

Focal necrosis in cotyledon (toxoplasmosis)

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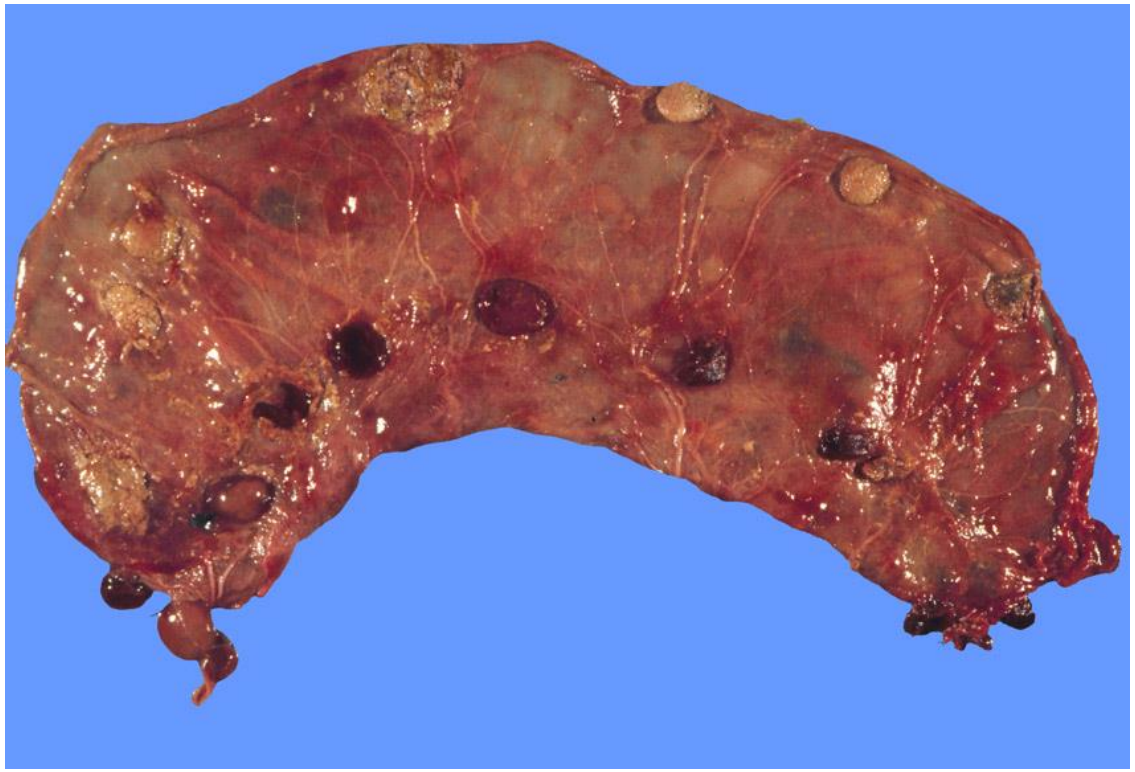
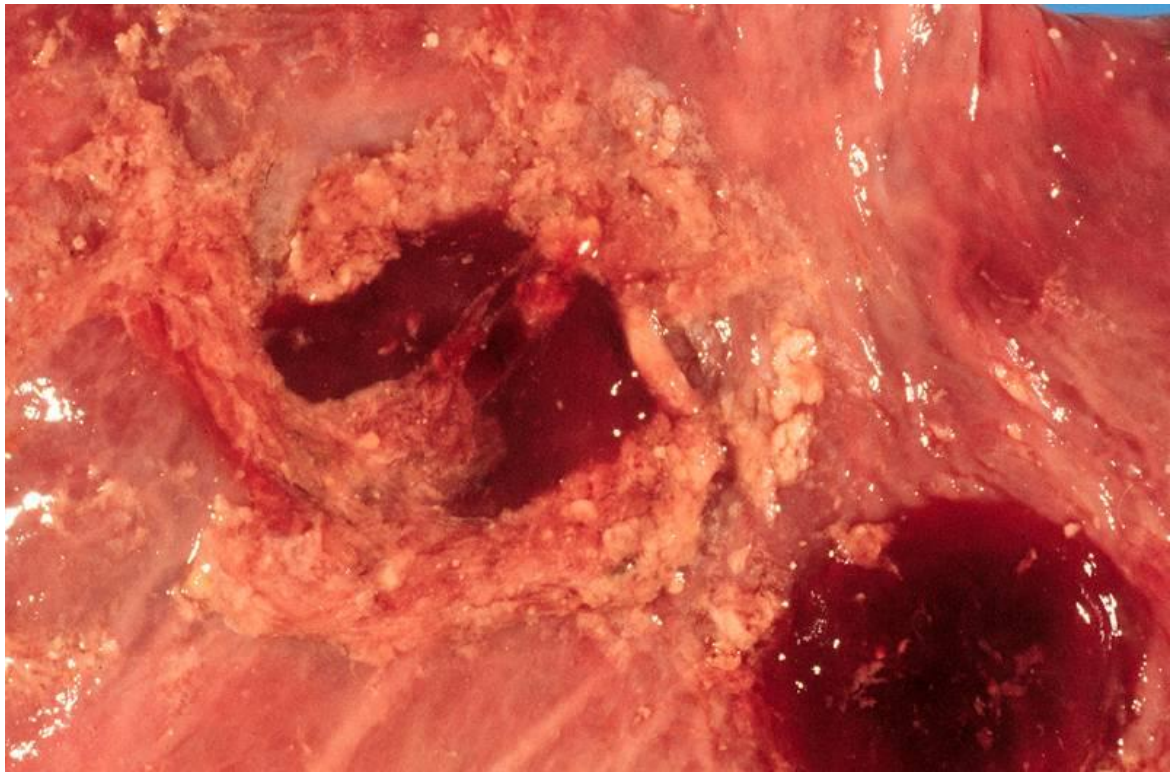
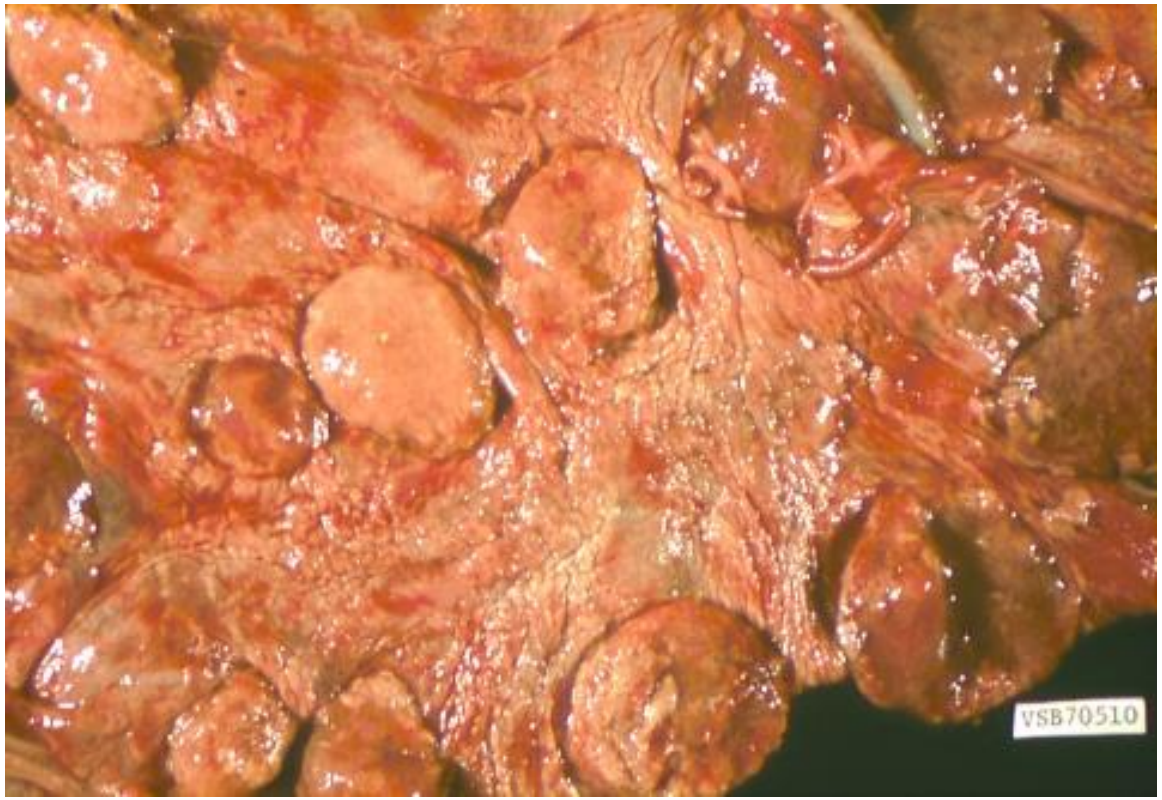
Placental Lesions: Chronic placentitis The 3 C's



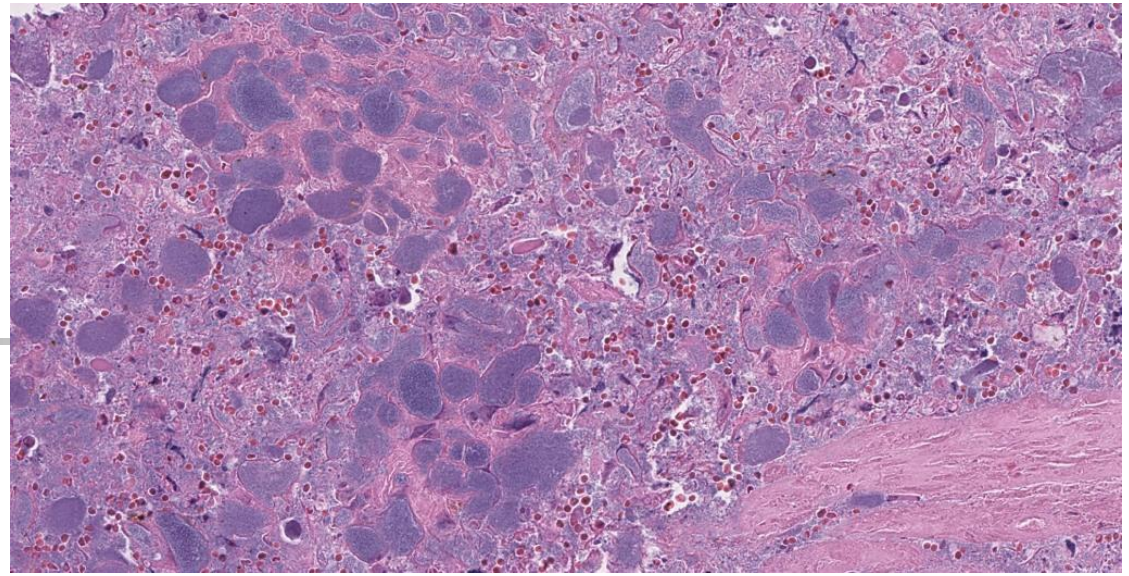


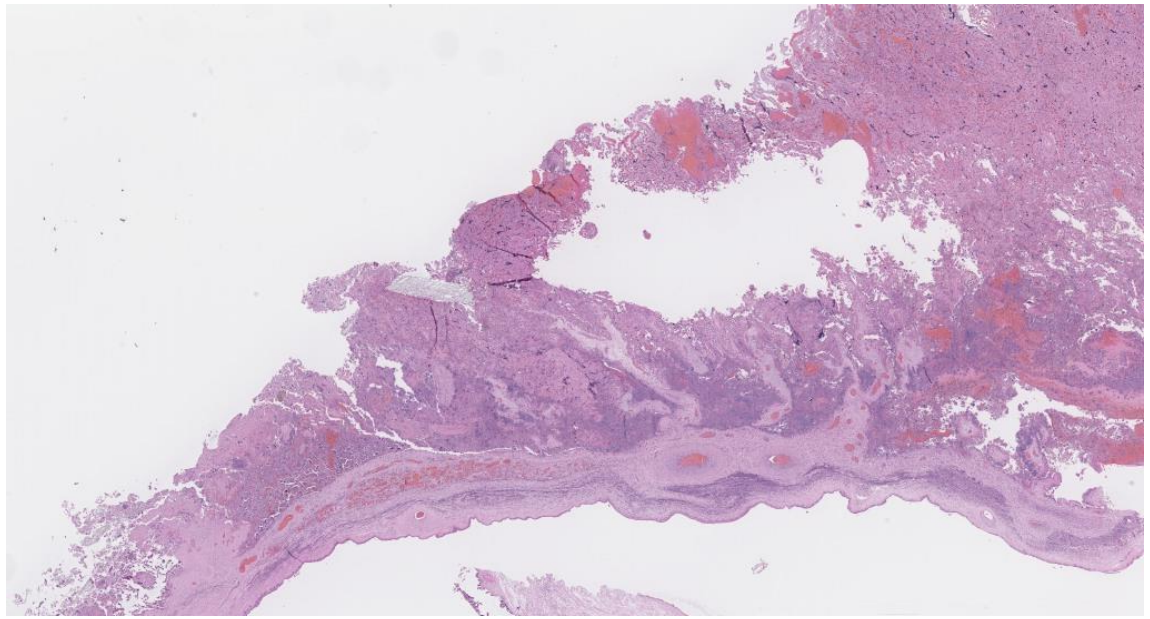
Placentitis

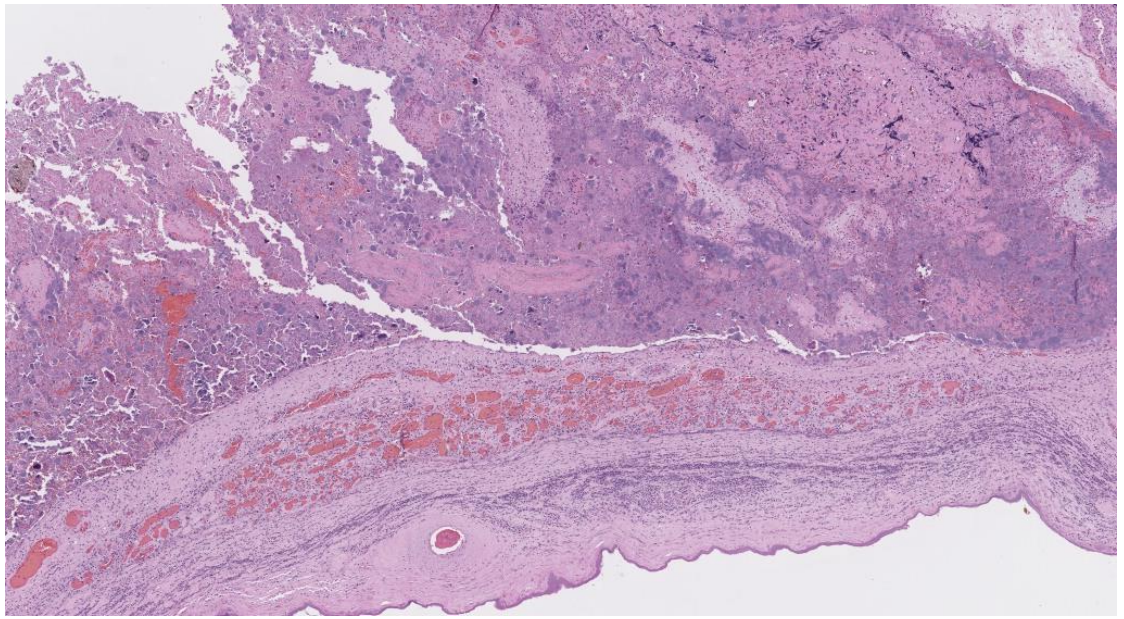
- edema
- exudate
- necrosis of cotyledon
- thickening of intercotyledonary placenta
- cupping of cotyledon



Placentitis





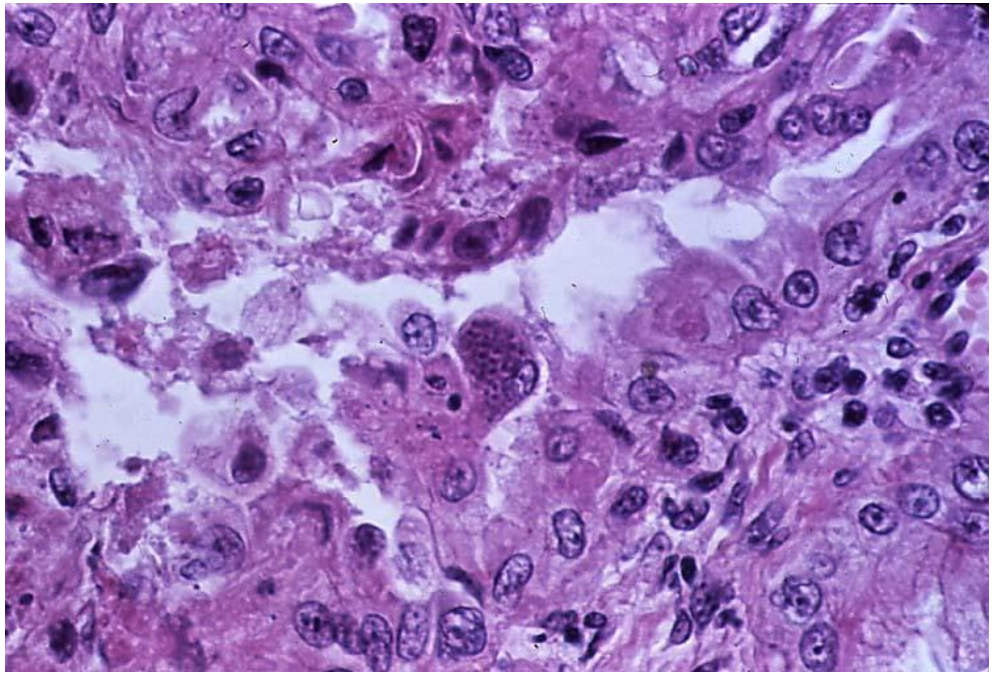


Pathogenesis of Placentitis

- Exposure of mucous membranes
- Local proliferation
- Bacteremia
- Localise in endometrium/placenta, fetomaternal interface.
- Trophoblasts around placentome especially infected
- Logarithmic growth of organism
- Necrosis, neutrophilic inflammation
- Failure of pregnancy

- Incubation
  - Coxiella -
  - Chlamydia – 50-90 days
  - Campylobacter – 7 - 60 days

Placental Lesions:
Toxoplasma gondii



Focal necrosis in cotyledons

Toxoplasma gondii

- Cat – rodent lifecycle
- Cat sheds oocyts for 7 days post infection
- Herbivores infected from contaminated feed – stored and pasture
- Adults develop immunity
- Infection during pregnancy
  - Placental and fetal infection
  - Abortion with characteristic lesions, mummification, stillbirth, weak lambs

Canine and Feline Failure of Pregnancy

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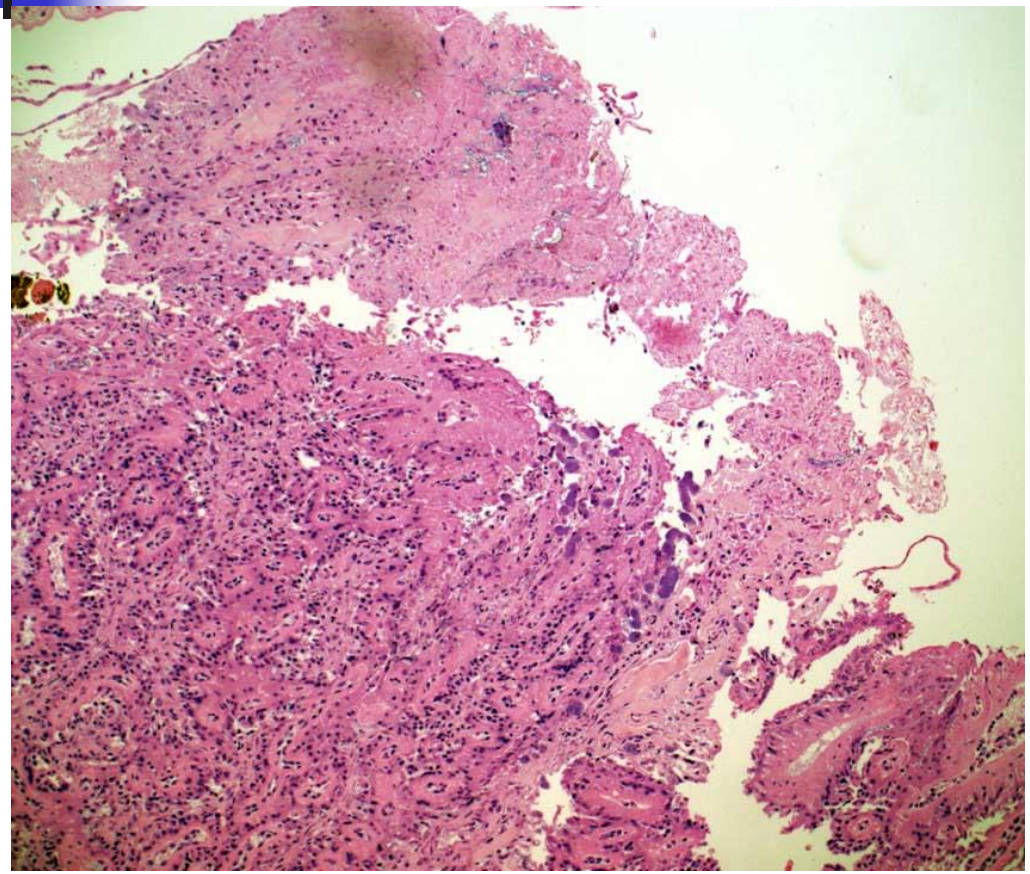
Public health issue - zoonotic disease

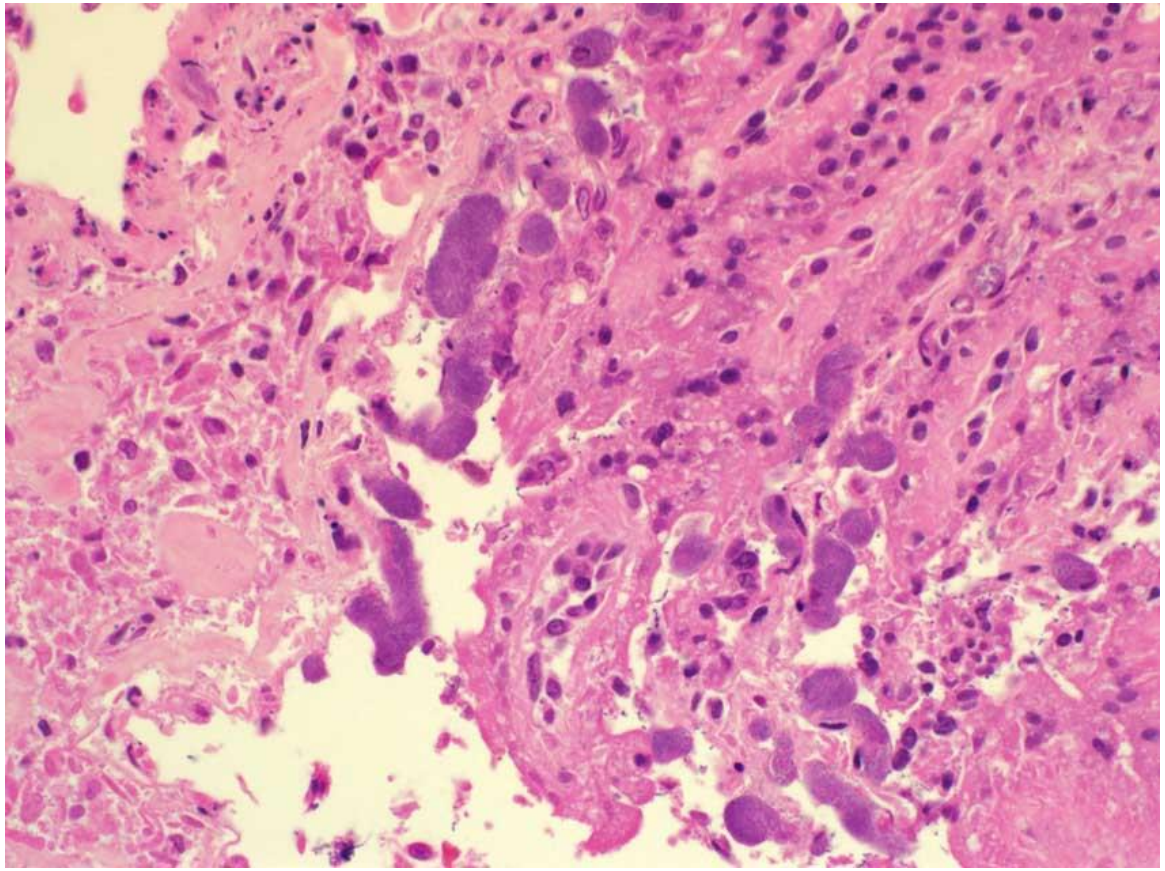
- List of zoonotic agents for dogs and cats is the same as for all species (general FOP).
  - *Campylobacter jejuni* and *Salmonella* occurs with some frequency
- In dogs *Brucella canis* is zoonotic
- Pregnant cats subclinically carry *Coxiella burnetii.*
  - Poker players pneumonia
  - Caesarian section vet clinic - morbidity.

Reported causes of FOP in dogs

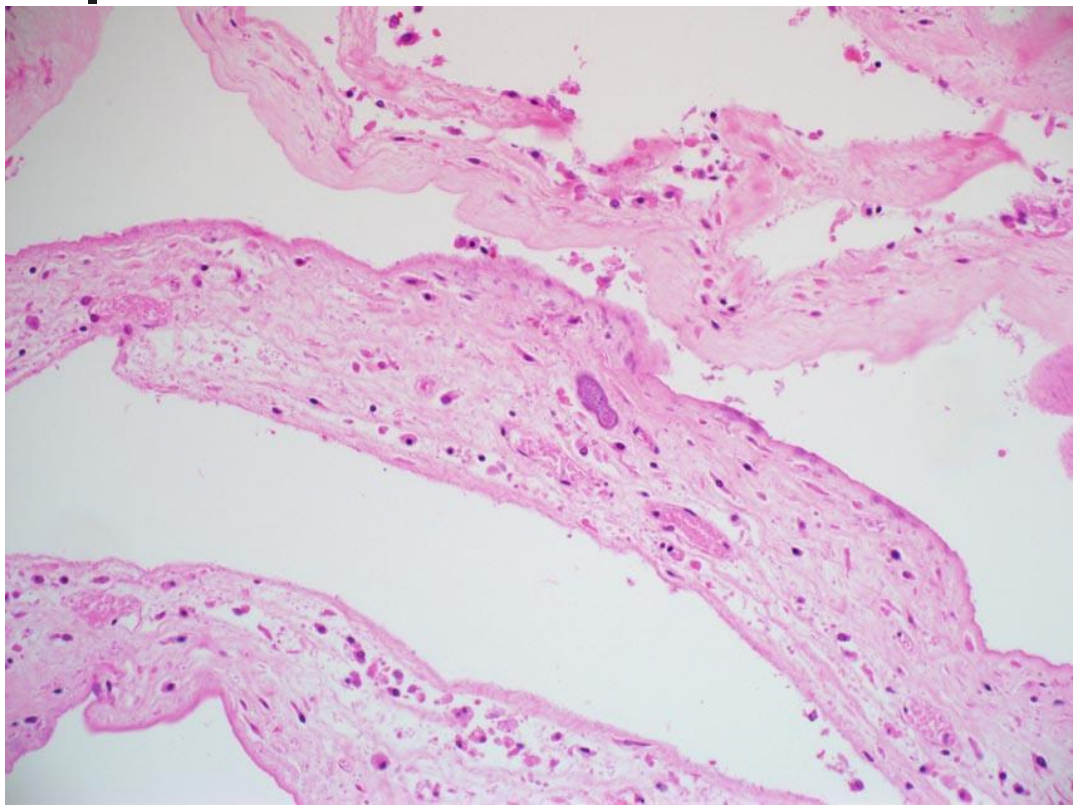
- Bacteria
  - *Brucella canis*
  - *Streptococcus* spp
  - *Salmonella*
  - *Campylobacter*
  - *Mycoplasma| Ureaplasma*
- Viruses
  - *Canid alphaherpesvirus 1* (canine herpesvirus 1 CaHV-1)
  - *Canine morbillivirus* (canine distemper virus)
  - *Canine mastadenovirus A* (canine hepatitis virus)
- Protozoa
  - *Toxoplasma gondii*
  - *Neospora caninum*
- Endocrine
  - Progesterone deficiency (hypoluteism)
  - Hypothyroidism

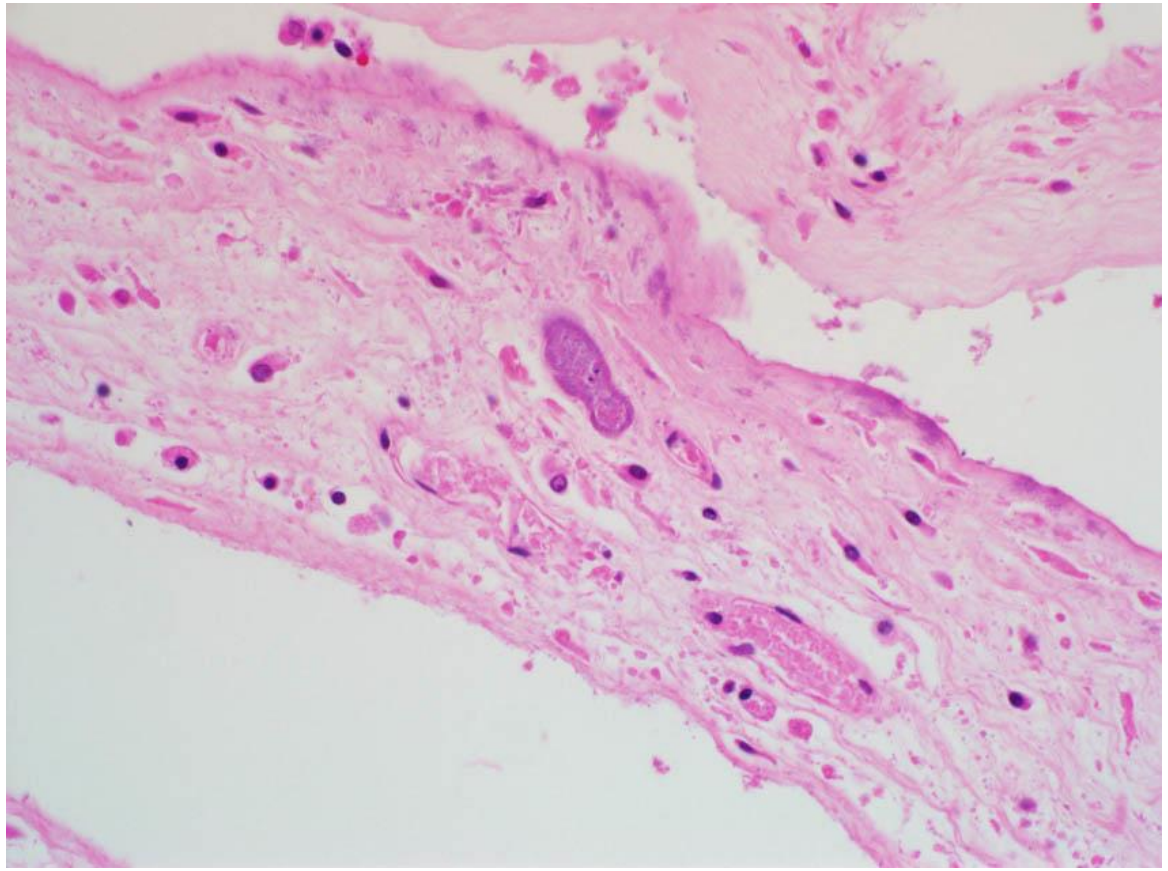
Canid: fibrinous placentitis





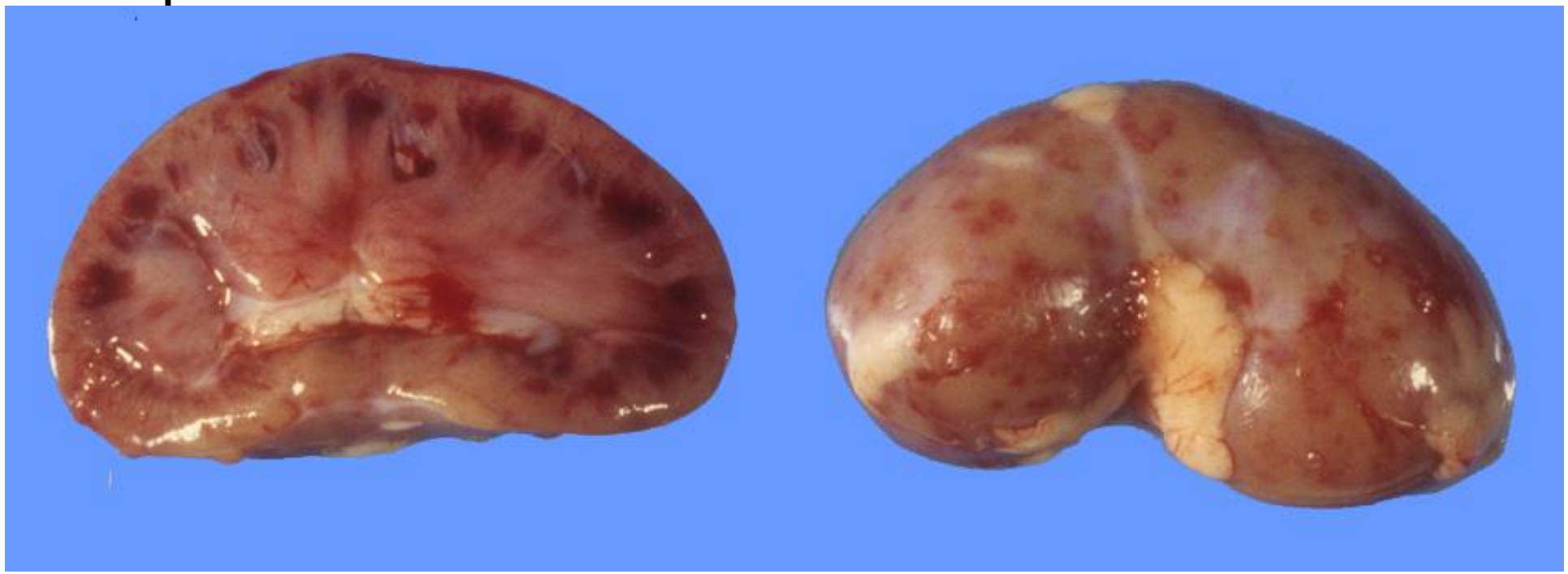
Canid: histiocytic placentitis with bacteria



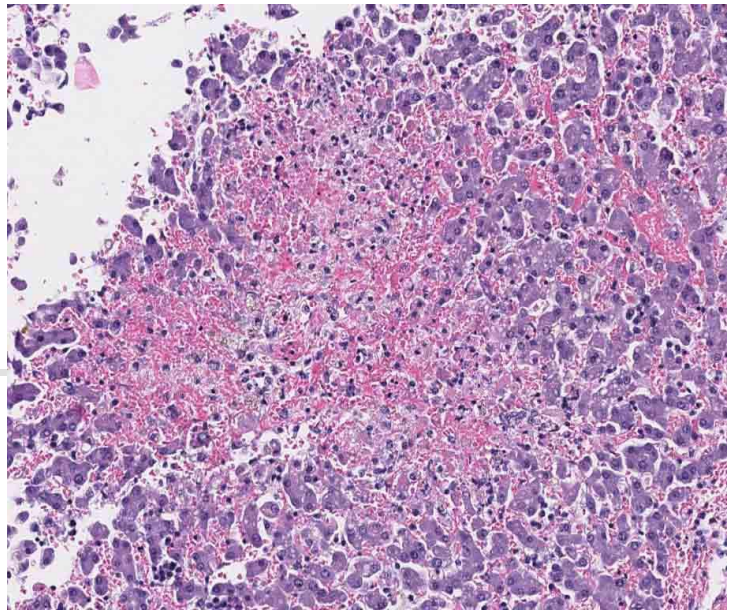


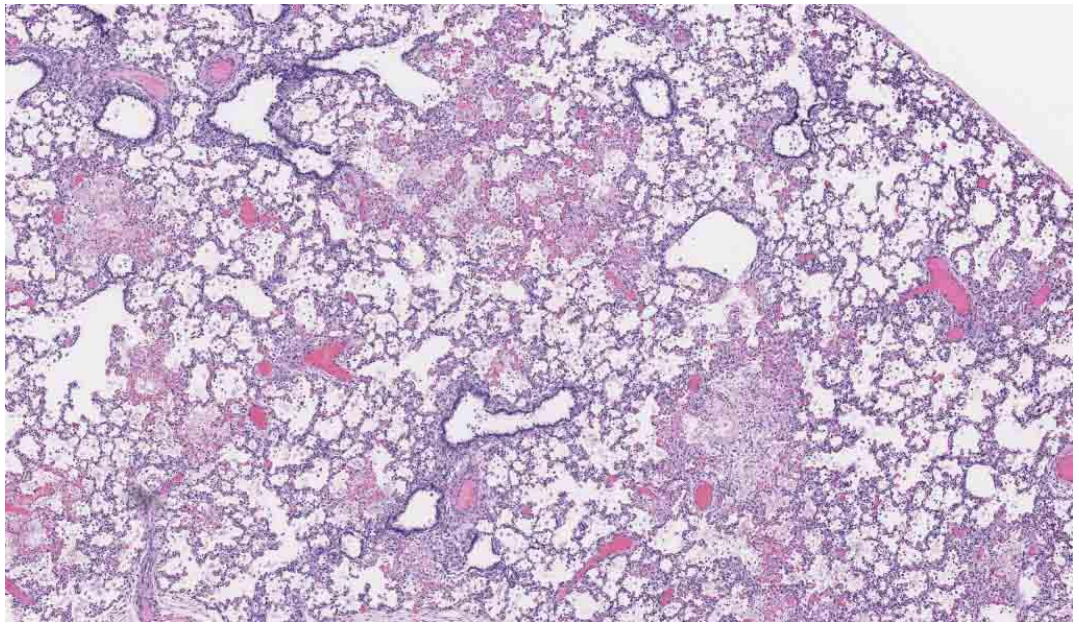
Canid alphaherpesvirus - 1

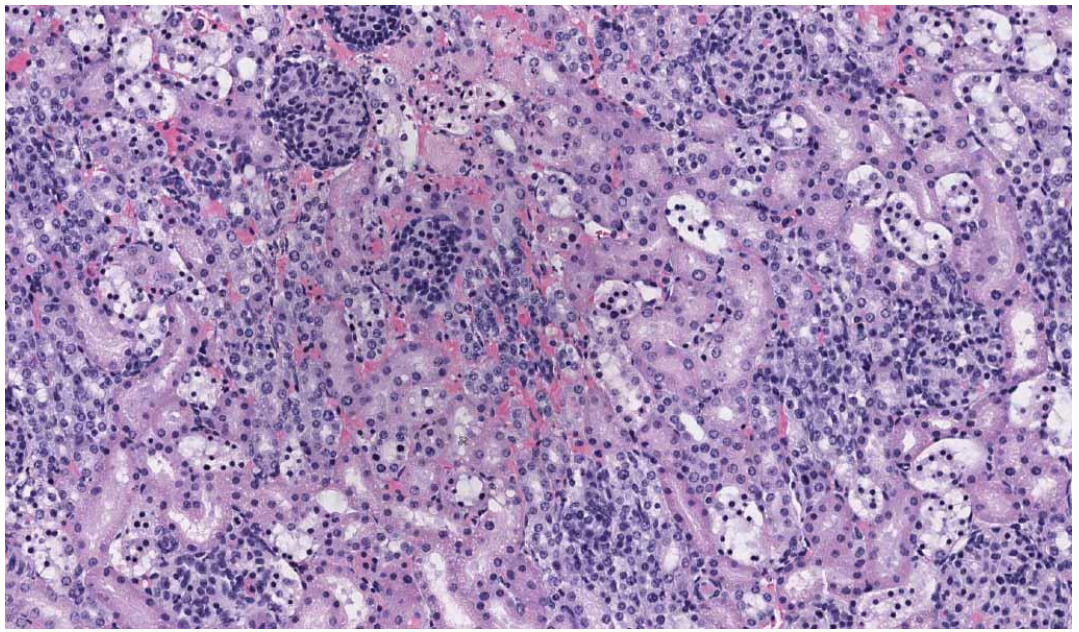
- Neonates to 4 wks
- Temperature 32^0C



Canid alphaherpesvirus 1







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Reported causes in cats

- *Felid alphaherpesvirus 1* (feline herpesvirus 1)
- *Feline calicivirus*
- *Feline immunodeficiency virus*
- *Feline leukemia virus*
- *Salmonella*

- Always consider *Coxiella*.

Porcine Failure of Pregnancy

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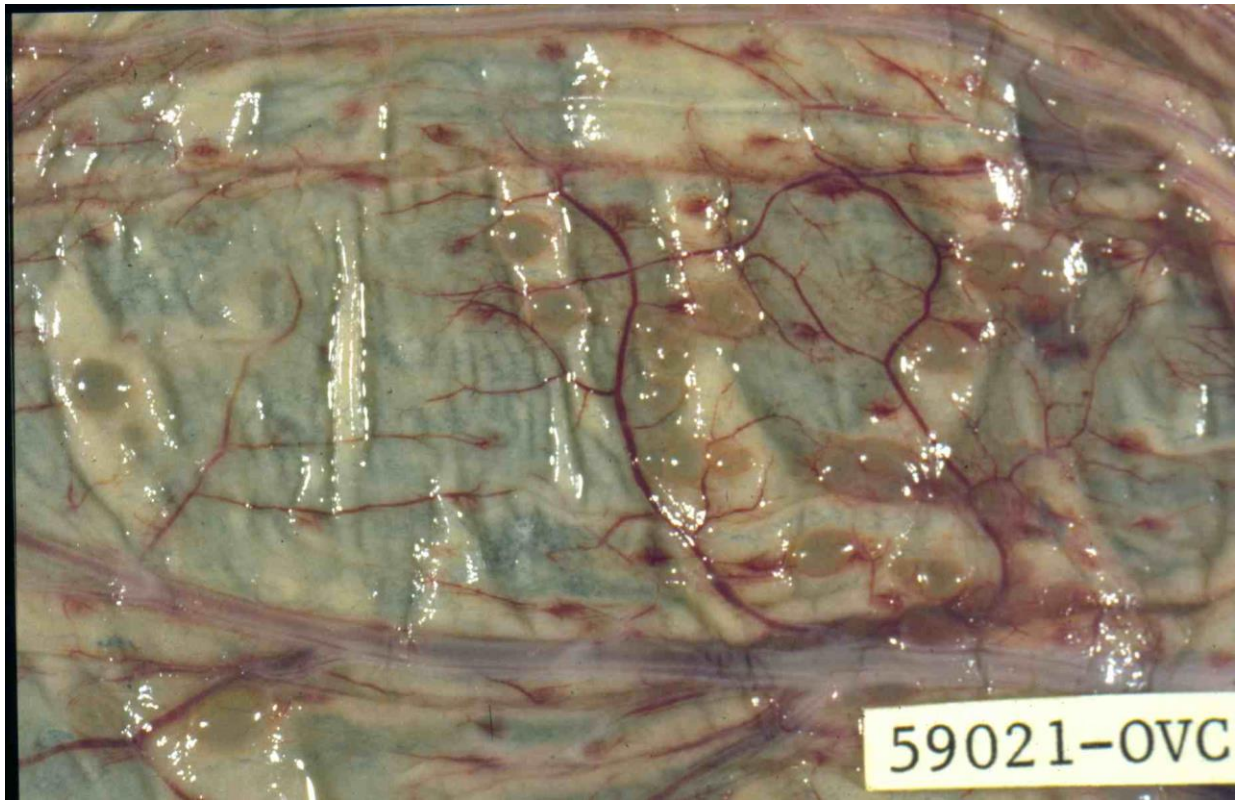
Pigs

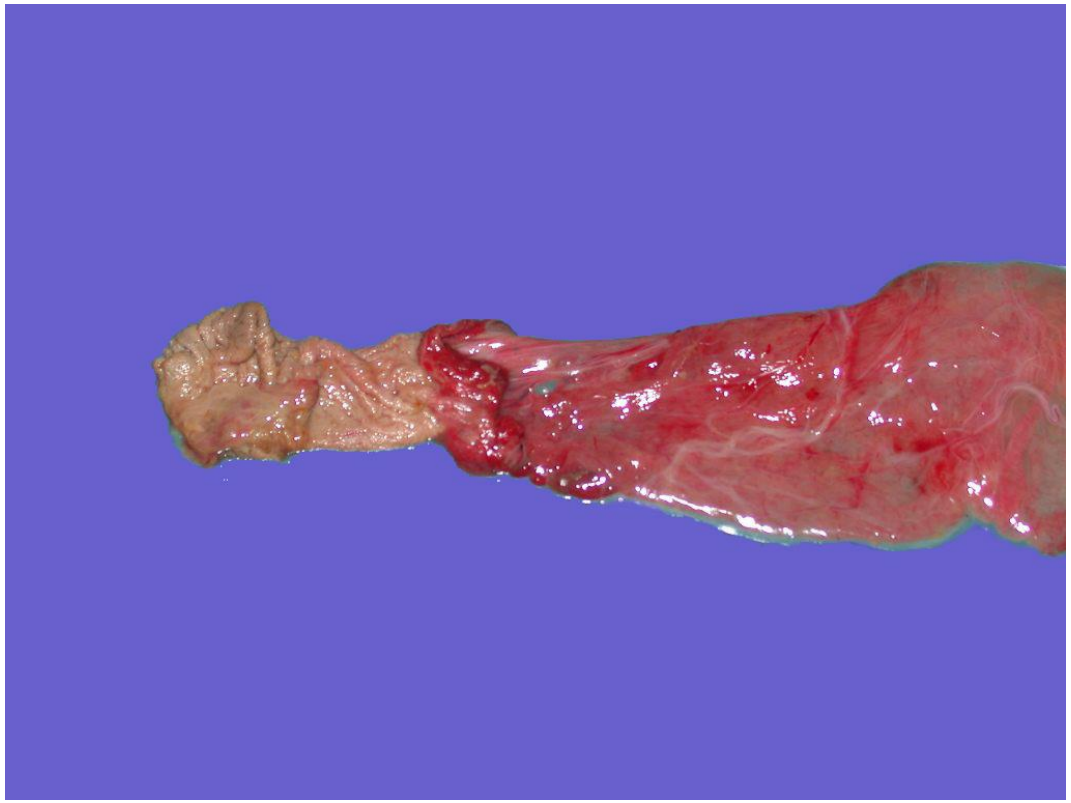
- No diagnosis 72
- Infectious 28
  - Porcine parvovirus
  - Porcine Reproductive and Respiratory Syndrome
  - Porcine circovirus 2
  - Leptospirosis

Specific differences

- large litter size and placental structure means competition for space - mummies, stillbirths, resorption.
- necrosis of tips of placenta normal.
- Chorionic cysts present
- much mineral

Porcine placenta - normal



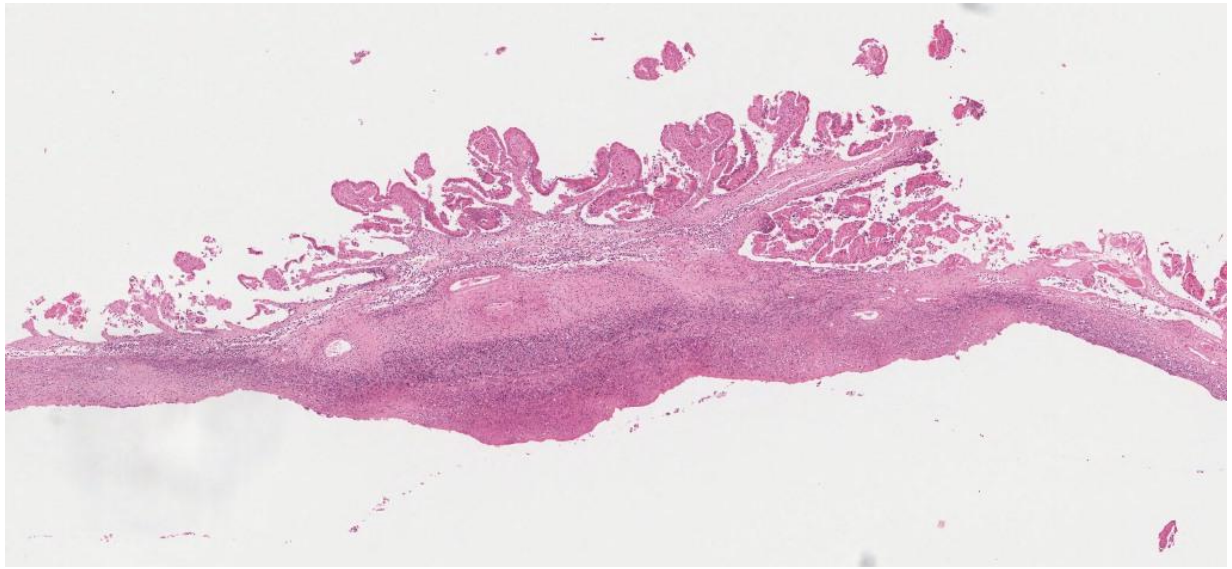


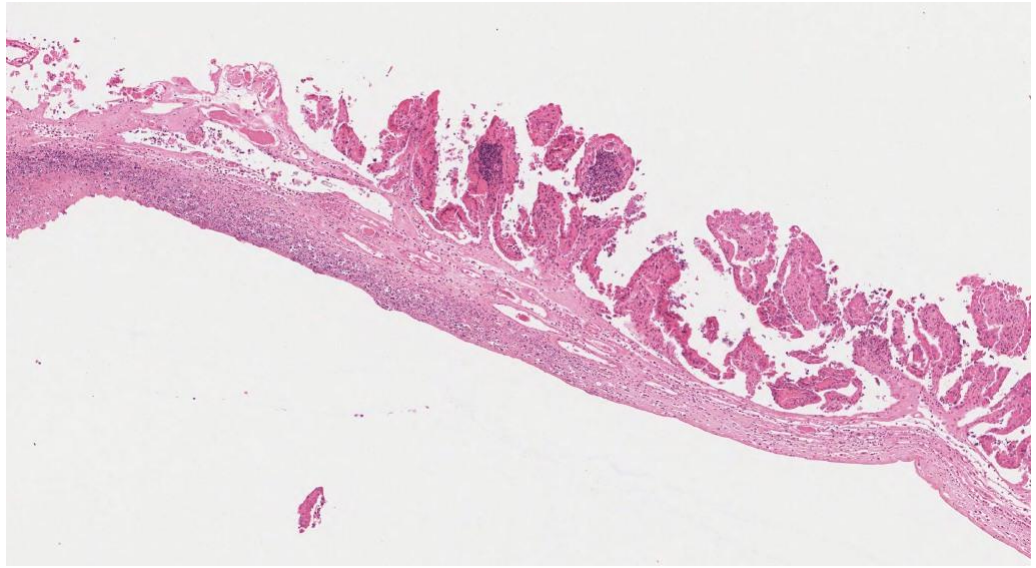
Chorionic cysts – and – necrotic tips of placenta

SMEDI

- Stillbirth
- Mummification
- Embryonic death
- Infertility

Porcine placentitis





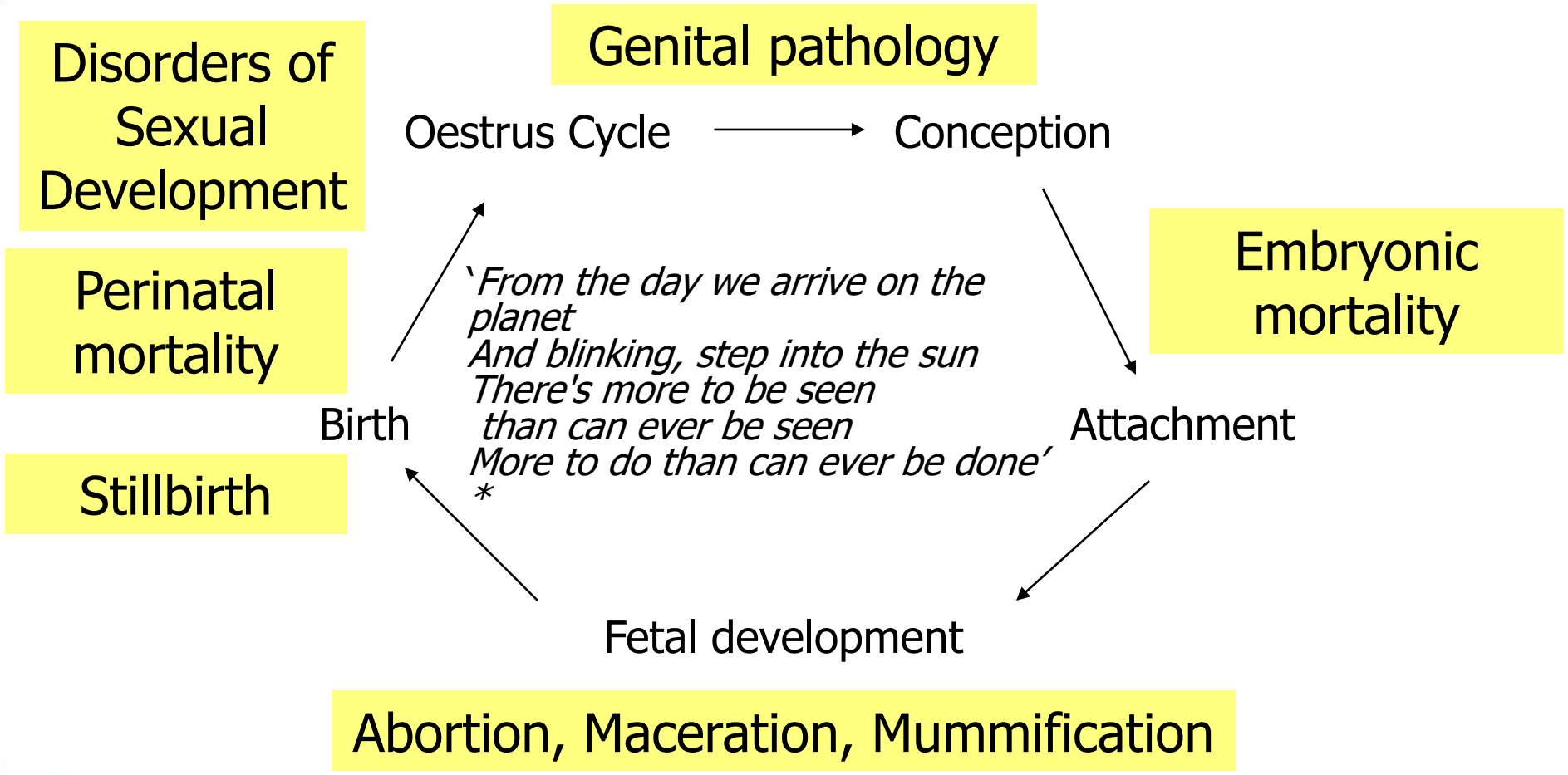
Summary

Disorders of sexual development

Female genital pathology

Failure of Pregnancy

Circle of Reproductive Life*



* "Circle of Life" Music by Elton John, lyrics by Tim Rice, Performed by Elton John

Principles of Reproductive Pathology

- Know normal anatomy and histology
  - Use species, breed and age matched controls
- Always correlate Macroscopic (Gross) Pathology with Histology
- Know what to expect!
- What happens in one species will happen in another

Know what to expect

- Common things occur commonly
- The number of diseases that affect one part of the reproductive tract is limited.
- Look for the normal you can recognise.
- Always look for macroscopic changes
- Chill and be methodical
- Recognise your fallibility – it is ok
- Know a friend to call/email/contact

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