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Unit 1 - Introduction and Intersex

Introduction

The reproductive system in veterinary medicine is fairly complicated. The differences in the reproductive system between the sexes and among species are complex. The temporal and physiologic features of the reproductive cycle vary greatly among species. And, with pregnancy, wow, there are SO MANY changes. No other organ system goes through as many dramatic changes in a short period of time.

At a minimum, the reproductive system consists of the gonads (testes or ovaries), and a duct system to the external environment. The gonads produce the gametes (sperm or ova) needed for sexual reproduction. The duct system varies in function depending on sex and species.

There are 3 different components to sexual differentiation:

- **Chromosomal sex** (=genetic sex) is normally determined at fertilization by the formation of either an XY or XX zygote. XX are genetic females and XY are genetic males. (You knew this already, I am sure).

- **Gonadal sex** means - does the embryo take those rudimentary non-gender gonads and turn them into testes or ovaries? Well, if there is a Y chromosome, the gonads become testes. The Y chromosome has an SRY (Sex-Determining Region on the Y chromosome) gene that codes for Testis-Determining Factor (TDF) and that is what urges the primordial genderless-
less gonad to become a testis. Without TDF that primordial sex-less gonad eventually goes female (ovary).

- **Phenotypic sex** - does it LOOK like a male or a female? Phenotypic sex is **determined by the male gonad** (or absence thereof). Testicular tissue secretes Müllerian duct inhibitory substance (MIS) that causes the Müllerian ducts to regress and the Wolffian ducts to continue development, into the vas deferens and epididymis. Then testosterone from the Leydig cells of the testis helps with all the other features of being male. Without testes producing MIS or testosterone, the Müllerian ducts continue to develop into uterus and oviducts and the Wolffian ducts regress.

What is intersex? It is any combination of two sexes in one individual. All are thought to be due to genetic problems, chromosomal abnormalities, or inappropriate hormone exposure. Sometimes we can figure out the reason and sometimes we can’t.
Terminology of intersex:

Hermaphrodite and intersex are more or less synonymous. About the only difference is the “hermaphrodite” is more scholarly-sounding, it being the marriage between two Greek gods and all.

Hermaphrodites (intersex) represents a broad grouping and the general term just means animals that have some of the characteristics (genetic, gonadal, phenotypic) of both sexes.

A true hermaphrodite has both ovarian and testicular tissue - at least one gonad containing ovarian and testicular tissue (i.e. an ovotestis) or has one male and one female gonad and exhibits anomalies of the external genitalia. This condition is RARE.

Pseudohermaphrodites are WAY more common. A pseudohermaphrodite has gonads of one sex and an anomaly of the external genitalia that resembles, to some degree, that of the opposite sex. Pseudohermaphrodites are further characterized as male pseudohermaphrodite if the gonadal tissue is male and as female pseudohermaphrodite if the gonadal tissue is female. The male pseudohermaphrodite is more common. Okay, a male pseudohermaphrodite - does it look like a female outside but has testes inside? YES! Pseudohermaphrodites are named according to their GONADS.

Some defined intersex conditions:

Freemartin
This intersex condition is seen in cows. A freemartin is a sterile female with underdeveloped ovaries born co-twin to a male. In cattle with multiple conceptions, the placental blood vessels usually fuse so that a common circulation develops between the fetuses.

There is “sharing” of cells due to these anastomoses resulting in permanent colonization of the female with cells from the male that express small amounts of TDF (testis determining factor), inhibiting ovarian development. In addition, MIS and testosterone secreted by the male inhibit development of the female tract. In ~92% of cases of mixed twins, the females are sterile. In freemartins, the ovaries are small and may contain seminiferous cords and Leydig-like cells. The tubular genital organs in affected animals range from cordlike bands to near normal uterine horns. In some cases, parts of the male tract may develop instead. Mammary glands are underdeveloped. The male twin is minimally affected.
**XX sex reversal:** This condition has been documented in dogs, pigs, goats, and mice. Even without a Y chromosome to initiate and sustain male development, these animals have some kind of recessive gene on the X chromosome that does the same thing. So some testicular tissue develops! Homozygotes have a testis or ovotestis, and some may morphologically appear to be males. Others are females with an enlarged clitoris and abdominal testes. In dogs, XX sex reversal is most common in American Cocker spaniels. Testicular tissue in these dogs lacks germ cells, and some dogs with an ovotestis and female tract have been able to produce litters.

My gonads are XY but something is wrong with my SRY gene. I look female but I’m probably sterile.

**Y sex reversal:** This condition has been reported in horses. It is an autosomal dominant inherited condition and may be a Y chromosome mutation. Animals are XY but they generally look like mares. The phenotype of affected animals is varied; there may be phenotypically normal but sterile mares, or individuals with ovotestes and underdeveloped tracts.

**Androgen insensitivity:** This syndrome has been seen in mice, rats, cats, cattle, horses, and humans. A mutation in androgen receptors renders cells insensitive to testosterone. They are genetic males but have more phenotypic characteristics of females. Many humans with this syndrome look very feminine.
Unit 2 - Ovary

Once an animal starts cycling, the size and form of the ovaries are altered by secretion of hormones from the ovary itself as well as the pituitary and hypothalamus. Here’s a quick pictorial review of physiology from last year:
DISEASES OF THE OVARY:

Disorders of development:

- **Ovarian agenesis** (no ovaries): This condition is most often seen in ruminants, pigs, and dogs. Ovarian agenesis can affect one or both ovaries and the associated tubular genitalia may be absent or underdeveloped.
- **Ovarian hypoplasia and ovarian dysgenesis**: Small, misshapen ovaries and usually the tubular tract is also underdeveloped and weird. This condition is seen most often in horses, it is Turner’s syndrome. Animals genetically are XO.
- **Ovarian remnants** (misplaced bits): Sometimes spayed animals still come into heat. For these animals, there are two possibilities. There may congenitally be small bits of ovary in some location other than the ovary OR during a spay it is possible that some incompletely removed snippets might remain in the abdominal cavity and continue to cycle. Oops.

Inflammation of the ovary:

**Oophoritis** (pronounced oh oh four eye tis) is ovarian inflammation. This condition is rare in most species and is usually due to a systemic bacterial infection.

Ovarian Cysts

Many types of cysts occur in or around the ovary. These include cysts of the ovary itself, of the fimbria that catch the eggs as they are ovulated, and mesonephric duct cysts (developmental remnants).

- Cystic ovarian disease comes in two types – cysts composed of follicles or cysts that are corpora lutea. The presentation and clinical problems are very different. In one case, there is way too much estrogen (follicular cysts) and in the other case there is too much progesterone (cystic CL). Clinical signs vary – with the former there can be prolonged estrus-like behavior OR anestrus, and with the latter, it is usually anestrus. Similarly, treatments are different.

Cysts around the ovary are pretty common in horses. They arise from embryonal remnants of other stuff. They usually do not interfere with fertility.
Ovarian neoplasia:

What are the kinds of cells that can become neoplastic in the ovary? Surface epithelium - these are adenoma/carcinoma; follicular lining cells - these are granulosa/theca cell tumors; and germ cells - these are called teratomas.

- **Ovarian adenoma/ adenocarcinoma:** These can occur in all species, but are most common in the dog. Adenocarcinomas can implant on the peritoneum (carcinomatosis) and obstruct lymphatics, resulting in ascites.

- **Granulosa cell tumors:** These occur in the horse, the dog and the cow. The tumors can get really LARGE! In mares, sometimes these tumors produce testosterone and the mare acts like a stallion. Because almost all these tumors are benign, surgical removal of the affected ovary is generally curative.

- **Teratoma:** These tumors originate from germ cell tumors that come from a single germ cell that has completed its first meiotic division. As a result, they can act as stem cells and have tissue of more than one embryonic germ layer. These tumors can be really wild, containing hair, bits of bone, teeth, etc. They are usually benign but rarely can be malignant. Here’s a teratoma with teeth!
Unit 3 - Uterus, Vagina, Vulva

The uterus of domestic mammals is composed of two horns, a body and a cervix. Histologically it is divided into the endometrium, containing endometrial glands, and the myometrium (which is the muscle). The main function of the uterus is to produce a protective environment for the conceptus in cases of pregnancy. The non-gravid uterus is relatively resistant to infection while under the influence of estrogen. The cervix provides an efficient protective barrier for the uterus. The normal cervix is closed during the luteal phase of the cycle and is patent during estrus.

Noninfectious diseases of the uterus:

Müllerian duct development arrest (segmental aplasia) leads to a variety of deformities.

- **Imperforate hymen.** The hymen forms where the paramesonephric duct merges with the urogenital sinus. There is a slight ridge or extra flap of tissue here as a result. For those animals with the least perfect fusion, the hymen is a flap of tissue that stretches to cover the caudal vaginal lumen. With complete obstruction by the hymen, secretions accumulate anterior to the obstruction and may result in development of a fluctuating swelling.

- **Segmental aplasia of the cervix** may result in mucometra (uterus fills with mucus) or cystic enlargement of the cervix.

- **Double external os of the cervix** occurs when Müllerian ducts don’t fuse. There may be a band of tissue caudal to, or in, the external os of the cervix. In other cases, there is a true double external os opening into a single caudal part of the cervical canal. Affected animals usually conceive normally. Sperm don’t care which door they go in. But there can be obvious problems at the time of parturition (“Help, there are two exits, which one should I take?...”) Or, maybe one foot in one, one foot in the other? Can you see how this creates big problems?

- **Segmental aplasia of the uterus** may involve one horn (uterus unicornis), both horns, or only part of one horn (which may result in cystic dilatation of the uterine horn anterior to the area of aplasia).
Uterine placement problems:

- **Uterine torsion**: This condition is seen in all species, but is most common in cattle. Cattle have a well-developed intercornual (between the two horns) ligament so when one horn twists, the whole uterus twists. It is most often secondary to pregnancy, hydrometra, or pyometra, i.e., something making the uterus HEAVY. Multiparous species without an intercornual ligament (dog, cat) may have only one horn or part of a horn twist. Twists over 180 degrees result in obstruction of veins, uterine infarction and fetal death if the animal is pregnant.

- **Uterine prolapse**: Prolapse of the uterus is most common in dairy cows and ewes. Recumbency with the hindquarters lower than the forequarters, excessive traction to relieve dystocia or retained placenta, uterine atony or hypotony, postparturient hypocalcemia, and consumption of legumes with high estrogen content, have all been incriminated as contributory causes. Prolapse of the uterus almost invariably occurs immediately after or within several hours of parturition, when the cervix is open and the uterus lacks tone. Occlusion of the vasculature as a result of the heavy uterus dangling out the hind end leads to infarction, necrosis and in some cases even gangrene.

Fluid and glandular problems:

- **Cystic endometrial hyperplasia (CEH)**: This condition is most important in the dog. It is part of a continuum - cystic endometrial hyperplasia/pyometra. In the dog the luteal phase is quite long, so there can be lots and lots of progesterone for quite a while after an estrogen surge and this might be what makes dogs so particularly susceptible to this problem. The uterus makes abundant mucus and if bacteria get in, they can grow very well and create pus.
Hydrometra/ mucometra: The uterus is filled with thin or viscous fluid. This condition is often associated with cystic endometrial hyperplasia. The other main cause is aplasia of some part of the caudal tubular tract resulting in trapped secretions.

Hydrosalpinx: Distention of the uterine tube with fluid, usually due to obstruction, such as with segmental aplasia, or following uterine irrigation in cattle causing inflammation and adhesion formation.

Subinvolution of placental sites (SIPS): This condition is seen almost exclusively in dogs. Normally uterine bleeding should stop 7 to 10 days after whelping. With SIPS, dogs may bleed for weeks or months, and develop severe anemia and sometimes fatal blood loss. After parturition, the trophoblasts just keep tunneling through the endometrium, and eventually erode through to cause hemoperitoneum.

Inflammation of the uterus/ uterine tube:
The majority of inflammatory lesions of the uterus begin in the endometrium as endometritis and are associated with either parturition or mating, both major disruptions to the normally cloistered
cells of the female reproductive organs. Infectious agents may enter the uterus as ascending infection from the caudal parts of the reproductive tract, or hematogenously. Ascending infection occurs especially in the mare.

**Terminology**
- **Salpingitis**: Inflammation of the uterine tube (Fallopian tube/oviduct). Usually an extension of endometritis and/or metritis. The poor oviduct - it is small and fragile and any kind of inflammation is likely to lead to scarring and obstruction. When this happens, the eggs cannot get to where they need to go to get fertilized.
- **Pyosalpinx**: Oviduct filled with pus. NOT common.
- **Endometritis**: Inflammation of the endometrium only (doesn’t go through to the muscle wall). Animals are not SICK, just can’t support a pregnancy.
- **Chronic endometritis**: The endometrium gets fibrotic, and glands are often atrophied. Periglandular fibrosis may result in cystic glands. Can result in infertility. This is a big problem in MARES (see below).
- **Metritis**: Inflammation of the ENTIRE uterine wall, like the muscle doesn’t work either.
- **Pyometra**: Pus filled uterus. Animals are very sick.

**Endometritis** is especially important in mares. Organisms gain access at the time of foaling or breeding, and set up a mild reaction in the uterine lining that causes an insidious fibrosis, making it impossible for the remaining glandular structures to proliferate sufficiently to support a successful pregnancy. Animals are not clinically ill, and vulvar discharge may be minimal, but the impact on fertility is substantial.

**Pyometra:**
**Pyometra** is seen in the dog, cat, and cow and rarely sheep. The uterus can be mildly to severely distended and filled with pus or foul smelling fluid. The endometrium is thickened, necrotic, and ulcerated, in addition to being hyperplastic and cystic. The serosa is congested. The wall is friable and may rupture.

**Another note about metritis:** Metritis might START OUT as endometritis, but with METRITIS, the inflammation has become more severe and now involves not only the endometrium but also some of the myometrium. Uterus is FLACCID. Animal is SICK.

![NOTE: With endometritis, animal is not sick, just can’t conceive or carry a fetus. With metritis, animal is sick as all get-out.]

**Diseases of the vagina and vulva:**

**Cysts:** In cattle, cysts are dilated remnants of Wolffian ducts called cystic dilations in Gartner’s ducts and Bartholin’s glands. Cysts can form following vaginitis, but also with cystic ovarian disease, and poisoning with chlorinated naphthalenes.

**Plus a few venereal diseases:**

- **Herpesviruses.** Herpesvirus happens in cattle and horses. Different viruses for each. It is venereally transmitted and results in blisters on the vulva and penis.

- **Contagious equine metritis** is a venereal disease of horses, resulting in mare infertility. The causative agent is *Taylorella equigenitalis*. There is a mild endometritis that keeps the conceptus from implanting.

- **Dourine:** This is also venereal, caused by a protozoan, *Trypanosoma equiperdum*. But this bad actor doesn’t just cause infertility. After wrecking the uterus and prepuce it goes on into the spinal cord and makes the animal ataxic.

**Neoplasia of the Uterus/ Oviduct:**
● **Leiomyoma:**
This is a benign smooth muscle tumor that occurs in all animal species but is most common in the dog. They are also common in women where they are called “fibroids”.

![Uterus and Vagina with Fibroid Tumors](image)

● **Leiomyosarcomas:** These are the malignant version of the leiomyoma. Like the leiomyoma, they can occur in the uterus, cervix, or vagina. They are less common than their benign counterpart. That’s good.

![Histology of Leiomyosarcoma](image)

● **Fibropapilloma:** This tumor affects the vulva of young cows. They are caused by infection with bovine papillomavirus. The masses are sessile and round to cauliflower like, basically “warts”. Most masses regress in 1 to 6 months.

● **Uterine adenocarcinoma:** These tumors can occur in all species, but are particularly common in old domestic rabbits and chickens. This tumor can spread hematogenously to the lymph nodes and lung. It can also spread by implantation (carcinomatosis) to the peritoneum. Carcinomatosis results in lymphatic blockage since the peritoneum is often covered with tumor tissue, impairing resorption of fluid, so animals will develop severe ascites.
Lymphosarcoma: This is the most common uterine neoplasm in the cow. Probably also the most common neoplasm in cows, period. It can be part of multicentric bovine lymphosarcoma or of primary uterine origin.

Vulvar squamous cell carcinoma: Similar to sunlight induced squamous cell carcinoma at other sites (periocular), squamous cell carcinomas of the vulva are most often seen in cows, horses, and ewes. They are typically locally aggressive, but are slow to metastasize to regional lymph nodes.

Transmissible venereal tumor:
This is a transmissible tumor that can be seen in all canidae including dogs, jackals, foxes, and coyotes. TVTs are macrophage origin tumors with an abnormal chromosome number, i.e., different from the regular dog number of chromosomes. It is transmitted by close contact including sexual, from one host to another. Clinically, there are one or more expansive, and often ulcerated and friable masses. The neoplasm normally regresses over several months and this regression is associated with T lymphocyte infiltrates so presumably the immune system eventually recognizes the cells as foreign and kicks them out.
Unit 4 - Diseases of the Pregnant Uterus

Pregnancy. The embryo moves into the uterus and implants, beginning to form a placenta. In animals that have cyclic estrus (cattle, sheep, goats, swine, and horses), the normal cycle HAS to get interrupted, that is, the corpus luteum has to KEEP ON GOING rather than regressing. Because the embryo needs progesterone in order to be able to implant and thrive.

| ![Cow] | In ruminants, the blastocyst prevents release of prostaglandins which normally work to lyse the CL. The blastocyst makes interferon gamma which prevents the synthesis of PGF2α from the endometrium. In the last half of the pregnancy the fetus and fetal membranes provide the progesterone needed. |
| ![Horse] | In mares, the embryo causes the formation of **endometrial cups** which are raised plaque-like structures in the endometrium and these supply equine chorionic gonadotropin from day 35 through 100 of gestation. This chorionic gonadotropin stimulates CLs to form in the ovary and so the ovary is responsible for producing the needed progesterone until 140 days of pregnancy at which time the fetal chorion takes over the production of progesterone. |
| ![Dog Cat] | In dogs and cats, there is no cyclic estrus, so the CL just keeps on going independent of whether or not there is a pregnancy. No problem. Except that this makes them much more susceptible to cystic endometrial hyperplasia/pyometra complex. |

**Loss of embryos** before you even know there is a pregnancy (30-35 days in large animals) is termed **Early Embryonic Death** (EED). It is estimated that as many as 30% of pregnancies in ALL species are terminated by EED, and that the cause of MOST of these are chromosomal abnormalities. But we really don’t know for sure because the tiny embryos are so small that they just get resorbed or if shed we don’t even see them.

**Fetal death**

(always) If there is EED, we don’t usually know it. There is delayed return to estrus and large animals may be “open” at pregnancy palpation.

- Fetuses that die a little bit later may be mummified, macerated, or aborted.
  - Mummification of a fetus usually happens in multiparous species - one of the fetuses dies but the others maintain the pregnancy. The dried up, small dead fetus is delivered at the same time as the others. There is no bacterial infection. If there were,
the fetus would be macerated consisting only of fluid and fetal bones (wet and gooey due to the action of the bacterial enzymes).

- Maceration of fetus occurs when the fetus dies and bacteria get in. There are usually complications of infection of the uterine lining as well.

- Abortion is defined as the expulsion of a fetus prior to the time of expected viability.
- Stillbirth is a dead fetus delivered within the period of expected viability.

**Placentation:**

Placentas vary considerably based on species and are classified in two main ways:

*Based on AREAS of connection -*

- **Diffuse:** horse
- **Cotyledonary:** ruminants.
  Cows have 75 to 120 cotyledons, sheep/goats have 40 to 125
- **Discoid:** primates, rodents
- **Zonary:** carnivores: dog and cat

![Diffuse, Cotyledonary, Discoid, Zonary](image)

In ruminants, cotyledons of the placenta interdigitate with caruncles of the uterus.

*Based on LAYERS of connection –*

![Layers of connection](image)

There is a total of six possible layers between maternal and fetal blood:

The three fetal layers ALWAYS remain but in some species there are fewer maternal layers, see below.
So, in the cow and horse, epithelium of the maternal uterus is apposed to the chorionic epithelial cells (all six layers, or \textit{epitheliochorial}). In the dog and cat, the maternal epithelium and maternal connective tissue have gone, so the chorionic epithelium of the fetus is directly in touch with the endothelium of the maternal blood vessels (\textit{endotheliochorial}). In humans and rodents, all the maternal layers are gone, so the maternal blood directly bathes the chorionic epithelium (\textit{hemochorial}).

Where is the fetus in relation to these structures?

This is a horse. So placentation is diffuse.
And for comparison, here’s the dog/cat model, with a single, circumferential band joining baby with mom.

And, ruminants, where there are discrete cotyledons on the outside

Specialized placental structures, mostly normal, but often mistaken for lesions:

- **Cervical star**: Area of equine placenta covering the cervix where placentation does not develop. Important area to check for inflammation/ infection ascending into the pregnant uterus. Cervical stars are NORMAL.
- **Adventitial placentation**: Extra placentation develops in between cotyledons in cows due to insufficient endometrial placentomes. A certain amount of extra placentation can be normal.

- **Endometrial cups** are seen in mares - they develop from fetal trophoblast cells, and are present from day 25 to day 100 of pregnancy. Endometrial cups produce equine chorionic gonadotropin (eCG) that stimulates continued progesterone production from secondary and accessory corpora lutea.

- **Amniotic plaques**: These are foci of squamous epithelium on the internal surface of the amnion. They LOOK like they should be abnormal but they are not.

- **Hippomanes** are soft putty-like brown/green flattened oval aggregates (maybe 10cm in length) found within the allantois of horses. They are masses of debris, especially especially fetal urine and cells. They are thought to bring good luck and it is said that if you should throw one up on the barn roof you will increase your happiness. Some farmers dry them out and carry them around in their pockets for luck.

**Retained placenta**: If the placenta is not expelled with 12 hours in the cow, and 2 hours in the mare, it is considered retained. All that nutritious material AND an open cervix – what bacteria could possibly resist? A retained placenta can predispose to infection and systemic complications.
Abortion and stillbirth

The difference between abortion and stillbirth when the pregnancy is very near term is slim. The most common cause of stillbirth is dystocia.

**Dystocia** is one of the most common causes of perinatal mortality, especially in large animals. The fetus has only a limited amount of time to make it through the birth canal. Once engaged in the canal, the umbilicus is compressed and so oxygenation is limited. It has to get through the canal and out into the environment and start breathing, or tissues will become hypoxic. Consequently many fetuses die on the way out. This can be very difficult to diagnose though. Here are some clues to figuring out if the fetus, which appears to be full-term, died during the passage out:

First of all, compare the size of the dam to the size of the fetus. Especially in younger, not yet fully formed moms, the first birth can be a rough one. In the fetus itself, look at the tissues of the head and neck. There may be significant cranial and facial swelling, but the most telling sign will be hemorrhage and edema of the subcutaneous tissues of the neck, just cranial to the shoulders.

See the photo at right - this is a dystocia. Usually the animals aren’t seen at this time though, the farmer walks into the barn in the morning to find a dead calf behind the cow.

Diagnosing **abortions** has a fairly low success rate. Even in the very best laboratories, the success rate for determining WHAT caused the abortion is often less than 50%. Often fetuses are so decomposed by the time they are expelled, that lesions are difficult to discern. Also, the placenta is often not available (eaten by scavengers), or has been sitting in fecal matter for hours prior to collection.

Abortion occurs most commonly in cattle and horses. Twinning is the most common cause for abortion in the mare. In horses there just doesn’t seem to be enough placental surface area to provide sustenance for two. Umbilical cord torsion is another common cause of abortion in horses. Other than twinning and umbilical cord torsion, both physical problems, in those cases where we diagnose the cause of abortion, it is usually infectious.

Here are some general rules about infectious abortions:

- Bacterial and mycotic infections usually compromise the placenta and starve the fetus of oxygen and nutrients, resulting in fetal death.
- Viral infections usually move right through the placenta, not harming it very much, but go on into the fetus and kill the fetus by viral infection of and damage to fetal organs.
- In general, mares get bacterial and mycotic infections of the placenta through the cervix.
- In general, cows get bacterial and mycotic infections of the placenta systemically.
Spread out the entire placenta and examine it in entirety. Look for areas of hemorrhage, necrosis, excessive mineral.

**Mummification/ Maceration**
Both of these are seen in animals that are multiparous - one fetus dies but the pregnancy continues because the other fetuses maintain it. In other words, although one fetus is dead, it doesn’t get expelled because the other members of the team want to stay where they are.

- In mummification, the dead fetus just slowly desiccates and shrinks and can look like a big very dry glob at parturition. It is sterile.
- Fetal maceration is similar, except that there is a bacterial infection (any old bacteria will do it) and it turns into a big GOOEY and STINKY mess that is expelled at parturition. If maceration goes on long enough, it can lead to a severe endometritis, metritis, or even pyometra. In the latter case, only the bones of the fetus will be present in the pus. Everything else has disintegrated under the power of the bacterial toxins and inflammatory cell enzymes.

**Infectious causes of abortion, by species -**

**Cattle**

**Opportunistic bacteria:** These are the “garden variety” pathogens, such as *Arcanobacterium pyogenes, E. coli, Pasteurella*, etc., that might just start a bacteremia for whatever reason, and find the placenta a particularly hospitable spot. Placenta has inflammation and necrosis. Fetus dies. Mother expels the dead fetus.
Opportunistic fungi: Mycotic abortion can be caused by a variety of organisms normally present in the environment. Infection is via hematogenous spread - they just happen to gain temporary access to the circulation and end up loving it in the placenta. Grossly, in mycotic abortions, the fetus is covered with multifocal plaques of hyphae and necrosis and hyperkeratosis due to fungal infection. Placental lesions are diffuse, and it has a dry, leathery look.

[Image of placenta and fetus]

Placenta is covered in thick exudate, mycotic abortion. Bovine fetus has fungal plaques on skin of head, mycotic abortion.

Brucella abortus – The Brucella bacteria live in the animal for a long time. If there is a pregnancy, they move to the placenta, which has a molecule called erythritol that allows them to grow very well. They grow so well there that they cause placentitis and abortion.

Bovine herpesvirus 1: This alphaherpesvirus is the causative agent of infectious bovine rhinotracheitis and infectious pustular vulvovaginitis. It can cross the placenta and get in to cause multifocal necrosis in a number of fetal organs. Fetus dies. Mom expels. Placenta looks just fine. Check the fetal tissues for multifocal necrosis.

Tritrichomonas foetus: This flagellate lives in the preputial cavity of the bull. Transmission is sexual. Females get cervicitis and endometritis, causing repeat breeding, abortion, or pyometra. Repeat breeding is due to embryonic mortality. Abortion is usually in the first half of pregnancy.

Bovine virus diarrhea: This virus may be the most complicated of all veterinary pathogens in terms of how it causes disease. There are so many outcomes of infection. Reproductive disease in infected cattle includes oophoritis (inflammation of the Madame Ovary), early embryonic death, abortion, mummification, stillbirth, birth of weak calves with or without congenital defects.
Sheep and goats -

**Toxoplasmosis:** *T. gondii* is another important cause of abortions, stillbirth, and neonatal death in sheep and goats. Felidae are the definitive host and the organism is often acquired from feed/pasture/bedding contaminated with CAT FECES. Parasitemia in the ewe leads to infection of the caruncle/cotyledon and then the fetus. In the placenta, only cotyledonary areas are necrotic.

*Coxiella burnetii* is a rickettsia that causes Q fever in humans and abortion in sheep and goats. It is strictly a placentitis that kills the fetus, with lesions predominantly in **intercotyledonary areas**, which makes it quite unusual. Smears will reveal abundant organisms. Be careful - the organisms aerosolize SO easily and people get infected readily through inhalation, with resulting encephalitis and myocarditis.

**Brucella melitensis** – The *Brucella* bacteria live in the animal for a long time. If there is a pregnancy, they move to the placenta, which has a molecule called erythritol, that allows them to grow very well. They grow so well there that they cause placentitis and abortion.

Sheep only -

**Chlamyphila abortus** *(formerly known as Chlamydia psittaci, ovine serotype; this syndrome is also known as Enzootic Abortion of Ewes or EAE)*: This organism is an important cause of abortion in sheep and goats.

**Campylobacter** spp. can cause abortion and infertility. The main species are *C. fetus* subsp. *fetus* and *C. jejuni*. These are intestinal infections, but the pregnant uterus becomes infected during transient bacteremia. The characteristic fetal lesion is multifocal necrotizing hepatitis that causes “target” lesions of central necrosis (dark) surrounded by cell infiltrates (lighter).

All ruminants

**Listeriosis:** Listeriosis causes abortions in cattle and sheep in the last trimester. This Gram positive rod causes a bacteremia in the dam and spreads through the placenta to the fetus.
**Bluetongue virus:** Spread by *Culicoides* insects, if infection in sheep or cattle occurs during critical periods of pregnancy, resorption, abortion, or stillbirth will occur.

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**Horses**

**Garden variety pathogens:** Bacterial infection of the placenta by just about any organism will cause abortion. In horses, these include beta-hemolytic streptococci, *Actinobacillus equuli*, *E. coli*, *Pseudomonas*, and *Klebsiella pneumoniae*. The main lesions are in the placenta - look for inflammation and necrosis.

In horses, the bacterial infection usually gets to the placenta via the cervix rather than through the bloodstream, as is the case in cows.

**Equine herpesvirus 1:** This is a major cause of abortion in mares. Abortions usually occur in the last 3 months of pregnancy. Virus in circulation of mom moves right through to baby. Baby tissues get necrosis and baby dies. The worst lesions are in the lungs of the fetus, but there is also multifocal hepatic necrosis. Placenta appears normal.

**Equine viral arteritis:** Caused by an arterivirus, this disease is spread venereally or aerosolization of respiratory secretions. This virus moves right through the placenta, killing the fetus, which is then expelled.

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**Cats and Dogs** - Abortions in dogs and cats are not common.
The male reproductive system consists of the testes (singular: testis), epididymides (singular: epididymis), prostate and associated tubular structures. The morphological and functional competence of the testis and epididymis is under the regulatory control of androgens. Mammalian spermatozoa leave the testis for the epididymis and vas deferens. Initially the sperm are immobile and incapable of fertilization. Factors that advance sperm maturity are present in seminal plasma derived from the accessory sex glands.

The testes perform two major functions that are largely complementary: the production of sperm and the secretion of steroid hormones (like testosterone). The steroid hormones influence the physiologic state of accessory ducts and glands and condition the appearance of the secondary sex characteristics, i.e. the male phenotype.

In most mammals, the testes normally descend into the scrotum shortly before or after birth and remain permanently in that position. The temperature within the scrotum is approximately 2-4°C lower than that of the abdomen. Both the interstitial cells (Leydig cells) and the germinal epithelium are dependent upon lower temperatures for maximum activity. Elevated temperature impairs enzyme systems of the mammalian testes and adversely affects spermatogenesis. The pampiniform plexus is a thermoregulator for testicular function and is indispensable for regulated optimal sperm proliferation.
**Tunica vaginalis:** This is an extension of the peritoneum into the scrotal sac so anything that affects the peritoneum can affect the tunica vaginalis. Peritonitis can extend down into the scrotum. When the tunica vaginalis fills with fluid, it is called hydrocoele. Also, because this cavity is continuous with the peritoneum, herniation of abdominal viscera, especially intestines, can happen in the tunica vaginalis.

**Testicular hypoplasia:** This condition occurs in all species, but is most common in cattle, sheep, and goats. The hypoplastic testis may be 25% normal size and is freely movable in the scrotum. The hypoplasia can be unilateral or bilateral. Histologically, the seminiferous tubules are small and lined by Sertoli cells alone or Sertoli cells and stem cells/ spermatogonia showing little to no mitotic activity.

**Cryptorchids** retain one or both testes somewhere along the path of descent. The undescended testicle may be located anywhere from just caudal to the kidney to within the inguinal canal. Testes retained within the abdomen suffer thermal suppression of spermatogenesis—the normal temperature of the scrotum necessary for spermatogenesis is 2-4°C below the normal body temperature.
Testicular degeneration: Testicular degeneration and atrophy are the most common cause for infertility in males. This condition can be either unilateral or bilateral. There are a large number of causes including:

- ionizing radiation
- temperature extremes
- trauma/inflammation/ infection (local or systemic disease)
- vitamin A deficiency
- zinc deficiency
- occlusion of spermatic vessels (spermatic cord torsion)
- blockage of epididymis and increased pressure or formation of sperm granulomas
- toxins (chlorinated naphthalenes, amphotericin B, gentamicin, carbamates, cyclophosphamide, locoweed, some mycotoxins)
- hormonal problems (neoplasms of the hypothalamus and pituitary, hypothyroidism, diabetes mellitus, Sertoli cell tumors that produce estrogen)
- advancing age

Sperm granulomas: Sperm are NOT recognized by the body as self so if they escape from the tubular structures to which they are supposed to be confined, there WILL BE a foreign body reaction! There are various causes of sperm getting out - obstruction, inflammation with rupture, and congenital malformations. The body’s response to sperm outside of the seminiferous tubules is a granulomatous reaction which can in turn cause obstruction.
Infectious diseases of the testis/epididymis:

Bacterial orchitis/epididymitis

Orchitis is rare in all domestic species. Epididymitis is slightly more common. In domestic animals, Brucella is often the most common cause of orchitis/epididymitis (*Brucella canis, Brucella abortus, Brucella melitensis*).

Neoplastic diseases of the testes:

What are the cell types in the testis that can become neoplastic? There are only three cell types - Sertoli cells (these are the cells that line the tubules and they secrete small amounts of estrogen), interstitial cells (these are the cells BETWEEN the tubules, also known as Leydig cells, these secrete testosterone), and germ cells.

What kind of tumors do they make? Interstitial cell tumors, Sertoli cell tumors, and seminomas.

All are very common in dogs, especially old dogs. The three of them occur with about equal frequency. And all are incredibly common in retained (cryptorchid) testicles. They are all mostly BENIGN.
Unit 6 - Accessory sex glands

The accessory sex glands all function for the same reason - to supply the fluid part of the semen. This is a short unit because there are very few diseases associated with the accessory sex glands. Accessory sex glands include: prostate gland, bulbourethral gland, and seminal vesicles - and their relative contributions vary with the species -

**Seminal vesicles are most important in ruminants and stallions; and prostate in the dog and cat.**

And, from the side:
Conditions affecting the accessory sex glands:

Seminal vesiculitis: Rare, seen most commonly in bulls and stallions.

PROSTATE gets many problems, mostly in DOGS –

- **Prostatic hyperplasia:** Usually occurs due to too many androgens. So, there might be a Leydig cell tumor in the testes! It causes constipation, and can interfere with urination. The gland is diffusely enlarged up to 4X normal size and may be nodular or have cystic areas.

- **Prostatitis** occurs when bacteria from the urinary tract move in because there is something very appealing about the prostate – maybe it is hyperplastic or metaplastic or cystic.

- **Prostatic cysts:** Big fluid-filled cavities in the prostate happen in association with hyperplasia, neoplasia or prostatitis. Can interfere with defecation.

- **Prostatic carcinoma:** Carcinomas of the prostate gland occur in older dogs. Bone metastasis common (one third of cases); they can also spread to viscera. Signs are often emaciation and rear limb dysfunction due to metastasis to the lumbar vertebrae. Grossly, an asymmetrically enlarged prostate is the most common finding.
Unit 7 - Penis and prepuce

Noninfectious conditions of the penis/ prepuce:

**Congenital hypoplasia:** An underdeveloped prepuce and penis may be associated with hermaphroditism, but several forms of hypoplasia not associated with hermaphroditism have been described in bulls (associated with shortening of retractor penis muscle). Hypoplasia may also be caused by early castration.

**Directional “deviations” of the penis:** *Persistent penile frenulum* is a common cause of penile deviation in bulls. This condition can also be seen in boars, dogs, and rarely other species. Congenital curvature of the os penis can cause deviations in dogs.

**Hematomas:** These can be from rupture of the corpus cavernosum or external trauma. It happens in young bulls and stallions.

**Paraphimosis:** This is the inability to retract the penis into the prepuce. It is seen most commonly in stallions associated with trauma, but any other cause of inflammation, neoplasia, or paralysis of the penis can cause paraphimosis. Phenothiazine tranquilizers (chlorpromazine especially) can also cause paraphimosis.

Infectious diseases of the penis/ prepuce:

**Balanoposthitis** is inflammation of the glans penis and prepuce. (Balanitis is inflammation of the penis and posthitis is inflammation of the prepuce.) The following are some causes:

- **Equine coital exanthema, infectious balanoposthitis (BHV-1), and dourine** were already covered under venereal diseases in the female. Each can cause lesions on the penis and prepuce.

- **Ulcerative posthitis:** This is seen in sheep, rarely in bulls. More common in wethers, it may be due to incomplete development of the penis and prepuce, and tendency for wethers to accumulate urine in the sheath. Also called “sheath rot”, or in a more colorful way, “pizzle rot,” it is caused by corynebacteria.
Neoplasia of the penis/ prepuce:

- **Fibropapilloma:** These benign tumors are seen in young bulls, 1 to 2 years of age. They are caused by bovine papillomavirus type 2 and are usually located on the glans penis. They can interfere with the movement of the penis - both retraction and protrusion.

- **Squamous papilloma:** These benign tumors are most common in the horse. There is also a transmissible genital papilloma of swine caused by papillomaviruses.

- **Squamous cell carcinoma (SCC):** Genital SCC is most common in the horse, but also occurs in dogs, and in cattle. Typically it affects the glans penis. In horses, stallions and geldings are equally affected. And there is a reported association with the accumulation of smegma, leading some to suggest that smegma is carcinogenic. Ulcerative and proliferative lesions can be extensive and cover most of the glans. Metastasis to the inguinal and iliac lymph nodes can occur, but only rarely does the neoplasm spread to other viscera.

- **Transmissible venereal tumor:** Already covered under the female section. This is a wild one.
Unit 8 - Mammary Gland

Developmental disorders -

Supernumerary teats or nipples are fairly common in many species. In cattle, as many as 30% of animals may have additional teats! Horses are the only species in which the male does not develop teats at all.

Inflammation

Inflammation of the mammary gland is called mastitis. It is a very important disease in cattle. Inflammation of the mammary gland is almost always caused by infection. And most infections occur by organisms moving up the teat canal. There are many defense mechanisms within the teat canal such as keratinization and acquired immunity. Normal milking does not cause damage but when the procedures or equipment are faculty (high vacuum, poor liners, ineffective pulsations, overmilking), there can be abrasions, eversions, and disruptions in normal bacterial flora that predispose to ascending infection.

Milk also has many products that help to decrease infection and these include

- lactoferrin that binds iron, making it harder for bacteria to get the iron they need
- lysozyme - kills bacteria
- lactoperoxidase - inhibits Staphylococcus and Streptococcus
- immunoglobulins
- phagocytic cells
Bovine mastitis

The normal skin of the mammary gland and teat have regular populations of bacteria which probably help to maintain an ecologic balance. *Corynebacterium bovis* and coagulase-negative staphylococci live here normally and in general keep the opportunists at bay. However, damage to the teat canal allows organisms access to deeper structures.

Staphylococci, streptococci, and the coliforms dominate the picture of bovine mastitis. Then there are some oddballs.

*Streptococcus and Staphylococcus* enter the mammary gland through the teat canal and find the glandular tissue a really great place to live and raise a family. Usually the cow is not sick, but the milk tastes horrible. Can’t sell it. Also production is lowered. A big problem with mastitis is that it tends to be permanent, hard to ever get the gland back to completely normal. So production is never fully returns.
Coliform mastitis

The organisms in this category that cause mastitis include: *E. coli, Enterobacter* spp., *Klebsiella* spp., *Citrobacter* spp., *Serratia* spp., and *Proteus* spp. All are part of the environmental flora and there is no predilection for mammary gland. They simply invade because the dirt in the environment is close to the open teat canal. “Hey, there’s an open door! I’m goin’ in!!!!” The damage that they induce is related to the **endotoxins** that they have (all are Gram negative and so have plenty of LPS). The microvasculature is shot and there are beaucoup neutrophils. Grossly the gland looks edematous, hemorrhagic, and there may be fibrin. If it goes on for long enough, there will be pus as well. It is usually restricted to one quarter but can rapidly destroy that quarter.

Mastitis in sheep and goats

- Mastitis in the ewe and doe is usually caused by *Staphylococcus aureus* or *Mannheimia hemolytica*. The latter can be very necrotizing and affects vasculature resulting in cyanosis and so is sometimes known as “blue bag”.
- Maedi-visna virus and caprine-arthritis encephalitis virus (CAE), both retroviruses, will cause mastitis in their respective species (sheep and goats).
Lactating goats that eat avocados develop mammary necrosis.

**Mastitis in dogs and cats**
Mastitis in dogs and cats is uncommon and is usually transient and due to staphylococci or streptococci.

**Mastitis in swine**
Mastitis-metritis-agalactia syndrome occurs in postparturient sows and is caused by a number of bacteria, most of whom are coliforms.

**Mammary tumors**

Mammary masses are very common in dogs and to a lesser extent, cats, but are rare in all other species.