

PATHOLOGY OF THE CANINE OVARY AND UTERUS - WHAT'S IMPORTANT, WHAT'S NOT

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Introduction:

This paper will address the nature and clinical importance of lesions of the canine ovary and uterus.

Ovarian lesions will be considered in 4 major categories reflecting the pathogenesis of lesions.

Pathology of the Canine Ovary

- 1) Abnormalities of Gonad Development
- 2) Changes Associated with the Estrous Cycle: Not to be Confused as Lesions
- 3) Acquired and Degenerative Changes of the Canine Ovary
- 4) Proliferative and Neoplastic Conditions of the Canine Ovary

Commonly encountered lesions of the canine uterus most frequently arise from the endometrium and are associated with abnormalities of proliferation. Uterine lesions must be differentiated from normal physiologic changes. Developmental anomalies other than those associated with intersex conditions are uncommon. Dramatic changes in the gross appearance of the uterus occur during the estrous cycle. Even more dramatic changes associated with placentation and pregnancy can at times cause confusion. These are of important clinical relevancy when reproductive organs are being examined by ultrasonography, endoscopy, radiography, abdominal palpation, or exploratory surgery. More precise assessment may require histopathology, but an experienced clinician can usually differentiate most lesions. Our discussion of uterine lesions will be organized in the following categories:

Pathology of the Canine Uterus

- 1) Abnormalities of Development
- 2) Changes associated with the Estrous Cycle
- 3) Endometrial Lesions Associated with Pregnancy
- 4) Acquired and Degenerative Changes of the Canine Endometrium (cysts, polyps, etc)
- 5) Proliferative and Neoplastic Conditions of the Canine Uterus

A) Pathology of the Canine Ovary

There is relatively little hard data in the literature concerning the incidence of ovarian lesions in the bitch. As would be expected, the harder one looks, the more one finds. Because the canine ovary is contained within a bursa, incision, or removal of the bursa is required for gross inspection. More subtle lesions are only evident after sectioning the ovary, and microscopic lesions are revealed when histopathology is performed. Small lesions can even then be missed and more detailed study frequently requires examination of a series of slides prepared from "step-sections" through the fixed and embedded ovarian tissues.

Gross Examination of the Ovary: Ovarian tissues removed either by surgery, or during necropsy should be carefully inspected, measured and palpated. Once removed, it is easy to confuse left from right, even if they are left attached to the uterus. By locating the opening of the ovarian bursa, one can tell the ovaries apart by placing the bursa medial-ventrally. This is the direction it faces in situ. The cranial and caudal ends of the ovary are identified by the suspensory ligament and convoluted venous plexus at the cranial pole and the proper ligament of the ovary that attached the caudal ovarian pole to the tip of the uterine horn.

Once the ovary has been examined, a single longitudinal cut along the greater curvature of the ovary, extending midsection through the center of the hilus should be made. This both provides a midline section for examination of the parenchyma, but also produced tissues that will fix quickly and thoroughly and can be oriented for histo-sectioning. It is important to use a sharp scalpel. The bursa can either be left on or removed, but should be submitted with the ovary. When the ovary is removed from the uterine horn, include a small piece of the tip of the uterine horn; both can be sectioned and included in the histology slide. If you think of the ovary as a bean shaped structure, you can make a very precise midline section as described above by simply picking up the ovary in its bursa and gently pressing it between your finger and thumb. This forces the ovary into a longitudinal, perpendicular position. By then starting your incision at the top outer edge of the tissues between your thumb and finger and cutting downward toward and onto a flat surface, you will end up with a well-oriented hemi-sectioned ovary. All pieces of ovary should be submitted as some lesions are focal and may otherwise be missed. Uterine tissue should always be submitted (opened or have instilled formalin into the lumen to ensure adequate fixation). Always include a full clinical history if submitting tissues for histopathology.

Dow examined 400 canine ovaries and described lesions in 115 (29%) (1). Such a high incidence of lesions, the obvious question quickly becomes, "Which ones of these are clinically relevant?"

1) Abnormalities of Gonad Development

A basic understanding of both normal sexual development and an appreciation of the morphological changes that occur in concert with these physiologic changes as they occur in the species in question are essential. Canine reproductive physiology is slightly more complex than that of most other species. Excellent references that address reproductive physiology of the bitch and queen are available (2-5). Diagnostic endocrinology testing is rapidly expanding and will continue to provide important insight into functional aspects of ovarian lesions making non-

invasive approaches more accurate and precise, however, clinical acuity is based on a firm understanding of reproductive physiology, anatomy and pathology.

We begin with a brief overview of the essential elements of embryonic differentiation of the gonads.

Ovarian agenesis: Complete absence of an ovary or ovaries is extremely rare. Likewise, ectopic tissue, referred to as "extra ovarian tissue" is also very uncommon, but has been reported (6) and may account for a small number of cases of the "ovarian remnant syndrome" (ORS) (6, 7). However, evidence seems to overwhelmingly suggest that feline (8) and canine (6) ovarian tissues detected after an animal has been neutered are usually the result of surgical error (8).

Ectopic Adrenal Tissue: Small tan nodules, representing ectopic adrenal tissue, are occasionally found within the mesovarium within a few centimeters of the ovary. Altera (9) reported on a series of 17 cases in cats. Microscopically these are composed of a capsule surrounding normal appearing adrenocortical tissue. In a retrospective study, ectopic adrenal-cortical tissue was identified in 2.2% of 499 cats undergoing routine ovariohysterectomy (9). Data on the prevalence in dogs is not available.

Intersex:: Abnormalities of the ovaries associated with intersex conditions occur as either small hypoplastic ovaries or abnormally appearing ovaries in "true hermaphrodites" in which male testicular tissues are also present (ovotestis). The genetics basis for abnormalities of sexual differentiation is complex, many breeds of dogs have heritable genes which are associated with development of intersex conditions. As a detailed discussion is beyond the limits of this paper, the reader is referred to reviews in the published literature (10-13)

The gross appearance of ovaries in intersex conditions can range from small hypoplastic ovaries, to gonads with the gross appearance of retained testes. There tends to be correlation between the amount of testicular tissue present microscopically and the gross features of ovotestes, associated ductal structures, and external genitalia. Close examination of the surface of an ovotestis will frequently reveal the presence of both a uterine tube and epididymis. Unless the gonad is entirely, or nearly entirely testicular, the ovotestis is usually contained within a bursa. A grossly visible epididymis and variable vas deferens are associated with the presence of significant amounts of testicular tissue within the ovotestis. Clitoromegaly and a ventrally located vulva are associated external features. Some bitches with ovotestis will have follicular development and can ovulate, therefore, follicles and corpora lutea may appear on the surface of the ovary. Microscopically ovarian and testicular tissues are typically located in different parts of ovotestes. This is because during normal female sexual development ovarian tissues develop within the cortical area; in the male, testicular tissue develops in the medulla.

2) Cyclic Changes: Not to be Confused as Lesions

Most bitches will cycle twice per year. Either follicles or corpora lutea will be present in the ovary for at least 3 months of each cycle, therefore one expects to be able to either see or feel these on the canine ovary at least half the time. The bitch is unusual in that follicles develop in the pre-estrous period start to luteinize prior to ovulation. Follicles when sectioned will have markedly folded inner granulosa cell linings. Recently ovulated follicles will have a bright deep

red hemorrhagic appear papillus over each ovulation site. Ovulation tags are uncommon in the bitch or queen. As the ovary of the queen can be everted out of the bursa, it is easier to conduct an ovarian examination that is the ovary of the bitch that has a smaller bursal opening.

Normal follicles will be multiple and of approximately the same size. This is helpful in differentiating normal follicle from any of the many cystic structures that can develop on or in or near the ovary. Normal mature preovulatory follicles in the bitch should not be larger than 8 mm.; (those of the queen will ovulate when approximately 3 mm in diameter). Animals with large cystic structures thought to be follicles can be checked for estrogenization of the vaginal mucosa to confirm they are follicles.

3) Acquired and Degenerative Changes:

Ovarian activity is driven by pituitary hormones. Ovarian function declines with age. Inactive ovaries are smooth and tend to be slightly smaller. Animals on chemotherapy or exogenous hormones may also have hypoplastic ovaries.

Ovarian Cysts: There are a number of cysts that can be found on the ovaries of cats and dogs. Their identification can usually be made based on the following features:

- Location
- Number
- Evidence of hormone production
- Evidence of changes in the inner wall
- Consistency of the fluid contained within the cyst
- Persistence

Cysts can arise from within or near the ovary from a great variety of structures. Data are not available regarding the relative prevalence of various ovarian cysts. Cystic remnants of the mesonephric and paramesonephric ducts and tubules are less common in ovaries of canine and feline than equine species, but are encountered with regular frequency in most diagnostic practices.

Cystic conditions of the ovary include:

1. Cystic Subepithelial Structures (S.E.S.)
2. Cystic Rete Ovarii
3. Follicular Cysts
4. Cystic Epoothoron, or Paroophoron
5. Tumors with Cystic Components
 - Cystadenomas of Surface Epithelium
 - Granulosa Cell Tumors
 - Teratomas

Cystic Subepithelial Structures (S.E.S.) arise from the normal infoldings of the epithelial cells (modified peritoneal cells) that cover the ovary in the bitch. Cells lining these structures commonly undergo hyperplasia and cystic distention. Their incidence increases with age. These

cysts may be single but usually appear as multiple clusters of cysts on one or more areas on the surface of the ovary. This is a helpful feature for identification of these cysts. It should be noted that this same tissue can undergo neoplastic transformation to become cystadenomas or cystadenocarcinomas. Cystic S.E.S. can become large, but usually do not affect ovarian function. The fluid contained in these cysts is clear and the walls are thin and transparent.

Cystic Rete Ovarii are the most commonly observed cysts in the cat and they do occur commonly in the dog. The rete tubules are branching structures that are always found near the hylar region in the ovary of the dog and cat. Because they develop from the rete ovarii (derived from mesonephric tubules) the cysts of the rete arise in the ovarian hilus. Microscopically, cysts of the rete will have small infolding of the walls of these cysts that represent the points of bifurcation of the rete tubules. Location, irregularity in size and histomorphology are important diagnostic features.

In the cat, these cysts tend to slowly progress and can become very large and can destroy the ovary, presumably by exerting pressure on normal ovarian tissues. Cysts of the rete ovarii in cats are one of the few cystic ovarian conditions in domestic animals that result in sterility.

Follicular Cysts are uncommon in the cat and dog although they are reported in both species. In one study, of 216 normal Beagles, ovarian follicular cysts were found in 3% of cases (14). They may be associated with abnormal estrous cycles. Vaginal cytology done over time may confirm persistent estrogenization.

Grossly follicular cysts contain clear fluid, but it may have a high protein content and gel when fixed. These cysts are larger than normal follicles [normal mature follicles are up to 3 mm in diameter and the queen and 8 mm in diameter in the bitch], and are usually multiple. They usually do not vary greatly in size.

A helpful diagnostic feature that occurs in follicular cysts is partial luteinization of the granulosa cell lining the inner cyst wall. This appears grossly as tan to orange tissue partially or completely lining the inner surface of the cysts.

Cystic remnants of mesonephric tubules are less common in cats and dogs than in horses, but can be found at either the cranial and caudal poles of the ovary. They are called “cystic epoophoron” when arising from the cranial clusters of mesonephric tubules and “cystic paroophoron” when arising from caudal mesonephric tubules. They are usually single, and tend to have smooth muscle in their walls, and therefore have a thicker heavier wall. They are considered incidental findings.

4) Proliferative and Neoplastic Conditions of the Canine Ovary

Two tissues of the canine ovary can undergo abnormal non-neoplastic proliferation. As noted above, the epithelium S.E.S. can proliferate and develop as grossly visible cysts. Some microscopically cystic changes are very common, as are small solid areas of S.E.S. epithelial proliferation. There can be referred to as "adenomatous hyperplasia" as they may appear gland-

like. The epithelium of the rete ovarii can also undergo excess proliferation. Neither of these are considered to be pre-neoplastic and neither is usually detected grossly.

There are 2 common primary tumors of the ovary:

granulosa cell tumors arise from granulosa cells lining follicles or atretic cords
- frequently produce hormones (estrogen), may be bilateral, commonly enlarge the ovary and contain cystic spaces, uncommonly metastasize

papillary cystadenoma or cystadenocarcinoma

- arise from S.E.S., equal frequency to ovarian granulosa cell tumor, may also arise bilaterally, benign forms may enlarge the ovary, carcinoma frequently penetrates through the surface of the ovary giving the ovarian surface a villous, "shaggy" appearance, may seed throughout the abdominal cavity (carcinomatosis)

Less commonly, tumors develop from germ cells or the theca:

dysgerminomas arising from germ cells - very rare in the dog and cat

luteoma-thecomas arising from luteal or thecal cells- also very rare

teratoma arising from germ cells

B) Pathology of the Canine Uterus

Gross Examination of the Uterus: First examine the entire tubular genitalia from the outside, looking for evidence of asymmetry then gently and carefully, using sharp instruments, incise the uterine horns, uterine body, cervix and vagina. Note any fluid contents. If abnormal, make smears for cytology and take samples for culture. Any tissue collected for histopathology should be free of crush, accompanied by the ovaries, and well fixed by either opening the lumen, or by carefully injecting a small amount of formalin into the lumen until slight distention.

1) Abnormalities of Development

Compared to other species, abnormal development is relatively uncommon, other than that which occurs as secondary to intersex conditions. Occasionally, shortened uterine horns occur. Rarely segmental aplasia of the uterine horn will result in distention of the proximal part of the horn with accumulation of tannish or grayish fluid and frequently concretions are found in the lumen. These are homogeneous and tend to have a "putty-like" consistency.

When the gonad is ovotestis, both the male and female ductal systems may occur together. If there are well developed uterine horns (paramesonephric duct derivatives) the presence of mesonephric (male) duct (this hypoplastic tubular tissue that would have been the vas deferens in a normal male) will be found in the wall of the uterine horns on the side where the broad ligament (mesometrium) is attached. Usually this tissue is most highly developed closest to the ovary, near the tip of the uterine horn. If it is present, careful examination of the caudal pole of the gonad will reveal a small epididymis (derived from mesonephric tubules).

2) Changes associated with the Estrous Cycle

Tissues that form the uterine wall, the myometrium and endometrium are very responsive to steroid hormones produced by the follicle (estrogen) and corpora lutea (progesterone). Marked edema and tissue growth and cellular hypertrophy and glandular secretion occur in response to these hormones. Additionally the luteal (secretory) phase of the estrous cycle of the bitch is very long, extending the time under which these tissue are under the influence of these trophic hormones. The uterine horns will enlarge by 1.5 times in diameter by the luteal phase of the cycle and the lumen will assume a cork-like shape. The associated tissue proliferation and shape change can make it difficult to insert a scissors and cut longitudinally along the horns.

In proestus, the mucosa is reddened and a small amount of free blood may be present in the lumen. The surface of the endometrium will appear moist and slightly rugose during estrus and the luteal phase of the cycle. Some mucoid material may be present.

3) Endometrial Lesions Associated with Pregnancy:

Embryonic Resorption: Death of individual fetuses from non-infectious causes usually result in their absorption; pregnancy for the remaining puppies progresses with no ill effects. The placenta will degenerate and be resorbed (appearing as pale to white caseous material) and the endometrium subjacent to the resorption will involute.

Placenta Percreta: An uncommon condition is excessive invasion of the trophoblastic cells of the chorioallantois that can penetrate the uterine wall in pregnancy. This can lead to rupture of the gravid uterus.

Subinvolution of Placental Sites: This is another pregnancy-related disease associated with abnormal trophoblast cell behavior. Following delivery, trophoblast cells persist into the involutionary period. They grown deep into the placenta bed and interfere with normal uterine healing. Their presence can weaken the uterine wall and result in uterine rupture.

4) Acquired and Degenerative Changes of the Canine Endometrium

Degenerative Changes: With aging, ovariectomy, or pituitary failure, the uterine horns will atrophy.

In queens and bitches that have had multiple litters, blood vessel between to 2 muscle layers of the myometrium will be very prominent. Endometrial glands may become distended and rarely lymphatics can also start to dilate. The amount of interstitial fibrous connective tissue will increase, and glands and blood vessels in the endometrium may become cuffed with encircling fibroblasts. This can progress with the deposition of fibrous connective tissue with encasement of individual glands by periglandular fibrous material.

Following severe pyometra, individual endometrial glands can be lost and replace with diffuse endometrial fibrosis.

Inflammatory Changes : Endometritis most commonly is found in the uterus when associated with cystic endometrial hyperplasia (the cystic endometrial hyperplasia-pyometra syndrome). The cellular response is initially lympho-plasmacytic and when bacterial proliferation progress, this changes to neutrophilic and suppurative endometritis. Controversy still exist about the role mycoplasma may play in uterine inflammation. Endometrial lesions of viral etiology are not well recognized.

5) Proliferative and Neoplastic Conditions of the Canine Endometrium

Proliferative Lesions of the Endometrium: Inflammation of the serosa on the surface of the uterine horns can lead to adhesion along the linear fold that occur in old bitches are those that have had litters. These can become filled with fluid forming "serosal inclusion cysts". These are either single thin walled cysts containing clear fluid or, more commonly, multiple cysts forming "grape-like" aggregates. These cyst usually are less than 1 cm in diameter.

Down-growth of endometrial glandular tissue into the subjacent myometrial muscles results in "adenomyosis". This ectopic glandular tissue can proliferate, become distended, and, if severe, leave of a "swiss cheese" appearance when the tissues are examined on cut surface.

Adenomyosis can weaken the uterine wall and may lead to uterine rupture during pregnancy. Occasionally the proliferation of ectopic glandular tissues is extensive and is termed glandular adenomatous hyperplasia. Adenocarcinoma of the canine and feline endometrium is rare.

Growth of endometrial tissue in the other direction, into the lumen of the uterus can occur focally, and when associated with interstitial fibrosis becomes endometrial polyps. A second type of non-cystic endometrium involves a highly regular remodeling of the endometrium which assumes histologic features of the endometrium beneath the placenta in a pregnant animal. The luminal surface is thrown into long villous folds and the glandular tissues assume uniform distention forming the equivalent of both the deep glandular and junctional zones of the gravid endometrium. The degree of tissue proliferation varies, from mild to dramatic. In the extreme, this may result in segmental distention of the uterine wall, appearing like a pregnancy site. This goes by different names: segmental endometrial hyperplasia, focal endometrial hyperplasia of pseudopregnancy.

Neoplastic Conditions of the Uterus: The most common neoplasm of the uterus of the queen or bitch is leiomyoma. There can take 3 forms: intramural, intraluminal, or expansile from the serosal surface into the peritoneum. They appear as single or multiple firm white clearly delineated masses. Rarely are leiomyosarcoma found. Reports of endometrial carcinoma are more likely placenta percreta or subinvolution of placenta sites.

6) Canine Endometrial Biopsy:

Methods of Biopsy Collection and Clinical Applications: There are two approaches: the most common and widely used is wedge or core biopsy take at laparoscopy. A second transcervical method had been attempted, but significant bleeding problems has limited this approach.

Adequacy of size and predilection for crush artifact associated with use of small biopsy instruments are of diagnostic concern. Biopsies are used to identify endometrial changes that

could interfere with conception and pregnancy. Changes such as endometrial fibrosis, inflammation, and gland loss have been shown to be of prognostic significance in other species. Based on our experience, this seems to hold promise for the canine.

What Types of Lesions Can be Detected? In addition to identification of fibrosis, inflammation and degenerative changes, biopsy can also shed light on cyclical state, endometrial atrophy, or, if collection is site specific, lesions within the endometrium and/myometrium (cysts, polyps, tumors, subinvolution, etc.) Controlled prospective clinical studies are needed to gain a better understanding of the merits and limitation of canine endometrial biopsy.

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