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Ovarian Disorders in Domestic Animals

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The histologic appearance of the ovaries and persistence of corpora lutea vary considerably among domestic animals, particularly between spontaneous and induced ovulators. The seasonally polyestrous mare has a variety of unique characteristics in ovarian structure and general reproductive function. Among the anomalies of ovarian development is the bovine freemartin with gonads containing a mixture of male and female elements. A variety of ovarian cysts occur in domestic animals, and persistent corpora lutea with associated reproductive perturbations occur in several species. Ovarian tumors are relatively uncommon in domestic animals, with most examples described in dogs, cats, and horses. These ovarian neoplasms are generally classified as epithelial, germ cell, or sex cord-stromal tumors.

Introduction

Investigations of ovarian disorders of the various domestic species were initially stimulated for rather different reasons. In food animals such as cattle, sheep, and swine, disorders of the ovary become economically significant when they adversely affect fertility and fecundity in these species; disorders that affect significant numbers of animals in a herd are particularly important. In the horse industry, individual animals can attain considerable economic value, and fertility of such individuals assumes great importance. In the small companion animals, such as the dog and cat, the veterinary profession's principal concern is to prevent reproductive function by castration; however, individual breeding animals can be valuable, and thus, economically justify investigation of their reproductive function. More recently, attention has focused on the comparative aspects of ovarian disorders in all domestic species, as an understanding of the pathophysiology of ovarian disorders in domestic animals will certainly provide information pertinent to similar disorders in women. This review will deal with several areas, including ovarian function in the different species (mare, cow, sow, bitch, and queen); nonneoplastic disorders of the ovary, including incidental lesions, developmental anomalies, oophoritis, and ovarian cysts; and neoplasms of the ovary.

Ovarian Anatomy, Physiology, and Incidental Findings in the Domestic Species

A knowledge of ovarian anatomy, physiology, and incidental lesions is essential to the understanding of ovarian disorders in each species. The histological appearance of ovaries varies considerably; the appearance is especially different in the mare. Persistence of the corpus luteum in nonpregnant animals and the importance of the corpus luteum in the maintenance of pregnancy also vary considerably between the species. Failure to recognize the unique features of the ovary in each species can lead to inappropriate and erroneous interpretation.

The bitch usually reaches puberty at 6 to 12 months of age, after which cycling occurs at an average interval of 7 to 8 months, although there is considerable variation between bitches. The bitch is a spontaneous ovulator and has a prolonged metestral phase. Regression of the corpora lutea is usually completed by postovulation day 75 to 80 in nonpregnant animals and commences about 24 hr prior to parturition (around day 62 of gestation) in pregnant bitches. Thus, the corpus luteum actually persists longer in nonpregnant than in pregnant bitches (*1*).

Reproductive disorders, such as cystic endometrial hyperplasia and pyometra, have previously been erroneously attributed to prolonged progestational stimulation of the endometrium from what were considered to be retained corpora lutea. In fact, cystic endometrial hyperplasia probably reflects exaggerated sensitivity of the endometrium to the influence of progesterone, because levels of progesterone and estrogen are similar in bitches with cystic endometrial hyperplasia and in normal bitches in metestrus (*2*).

The ovary of the bitch is characterized by the presence of cords and nests of cells beneath the surface epithelium, the so-called subsurface epithelial structures that arise from the surface epithelium. These proliferations are very prominent at certain stages of development in the fetal ovary and increase in number and prominence with advancing age in postnatal life. Hyperplasia and cystic dilation of these structures can

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occur, usually in geriatric bitches. Cystic dilatation and/or hyperplasia of the rete ovarii also occurs with advancing age (*3*).

Within the cortex and medulla of the canine ovary are cords of cells that have been termed pseudotesticular tubules or granulosa cell cords. Although these cords derive from atretic follicles and contain granulosa cells, cells in the cords often palisade at the periphery with a pattern reminiscent of that of Sertoli cell tumors of the testicle and the ovary. Granulosa cell cords are more prominent in the ovaries of older bitches (*3*).

The queen shares many features with the bitch, so only differences between the two species will be discussed. The queen is an induced ovulator, and like the bitch, has a prolonged metestral phase in its cycle; however, after a sterile mating, corpora lutea regress by about postovulation day 36. The corpus luteum of pregnancy persists longer and is essential for the maintenance of pregnancy until at least gestation day 46 (*1*). Interstitial glands are present in the stroma of the ovarian cortex, and these consist of aggregations of polyhedral cells with abundant cytoplasm that resemble luteal cells or interstitial (Leydig) cells of the testis (*4,5*). Cells in interstitial glands may be hormonally active; however, their function is poorly understood.

Puberty in the cow is more dependent on size than age, and restricted nutrition can delay onset of puberty. Malnutrition, thus, can adversely influence reproductive performance, with delayed onset of puberty being a problem not uncommonly encountered among cattle in economically underprivileged nations. The length of the estrous cycle in the cow is approximately 20 days. In contrast to the queen and bitch, regressive changes are apparent in the corpus luteum of nonpregnant cattle by postovulation day 18 (*6*). Dilated vascular channels (hamartomas) have been reported in the ovary of cattle (*7*). Tags of fibrous connective tissue (ovulation tags) are sometimes present on the surface of the ovary and are presumed to be organized fibrin that was released at ovulation (*8*).

The sow reaches puberty at 4 to 9 months. The length of the estrous cycle is similar to the cow, with a range of 18 to 24 days. Extensive regression is present in corpora lutea of nonpregnant sows by 17 days after ovulation, whereas corpora lutea are essential for maintenance of pregnancy throughout gestation in pregnant sows. Luteal and follicular cysts are sometimes found in the ovaries of apparently normal, pregnant sows (*9*).

The mare has a variety of unique characteristics in her ovarian structure and general reproductive function. The mare is seasonally polyestrous, and cycle length is variable (*10*). During fetal development, medullary tissue replaces much of the ovarian cortex, leaving a restricted area of cortex that becomes the ovulation fossa. Ovulation can only occur at this site (*11*). Follicles in the mare are large, up to 6 cm. Ovarian hematomas can result from hemorrhage into the follicular cavity after ovulation, and such hematomas can attain considerable proportions before they regress (*12*). The corpus luteum normally persists 14 days in the nonpregnant mare, but retention of the corpus luteum is not uncommon (*10,13*). The pregnant mare usually develops secondary corpora lutea between days 40 and 60 of gestation. The secondary corpora lutea are formed by either ovulation of luteinization of follicles that develop under the influence of gonadotropins released from the endometrial cups. Primary and secondary corpora lutea regress during the fifth or sixth month of gestation. After this time, the placenta becomes the major site of progesterone production (*10,14*).

The ovary of the mare contains considerable areas of stroma, consisting of interlacing bundles of spindle-shaped cells. Primary follicles are scarce (*5*). Within the parenchyma of many equine ovaries are nests of cells with abundant, vacuolated cytoplasm, which are considered by some to be ectopic adrenal cortical tissue. A large mass of ectopic adrenal tissue attached to the ovary of a mare was also described (*15*). Vascular hamartoma of the ovary has been reported in the mare (*16*).

Anomalies of Ovarian Development

Anomalies, such as ovarian agenesis and supernumerary and accessory ovaries, have been sporadically described in domestic animals. Fusion and abnormal location of the ovaries have also been reported. Ovarian hypoplasia associated with a deficiency of germ cells occurs infrequently, although an abnormally high incidence of the anomaly has been described in Swedish Highland cattle. The degree of hypoplasia can vary in individual animals (*8*).

A variety of forms of intersexuality have been described in domestic animals (*8,17*), and only brief mention will be made of these abnormalities. Perhaps the most famous intersex is the freemartin, a condition most commonly reported in cattle, but which has also been recognized in sheep, goats, and swine. The bovine freemartin is an infertile female twin of a normal bull. The gonads of the freemartin are a mixture of male and female elements, although the distribution of these elements is variable. Masculinized female gonads are termed ovotestes. The tubular genital tract is usually incompletely developed, and male secondary sex glands are present. The cause of freemartinism is unknown, but a recent proposal suggests that soluble H-Y antigen from the male fetus causes abnormal differentiation of the reproductive tract of the female twin. As a result of anastomosis of the placental vessels associated with each fetus, freemartins are chimaeric, having a mixture of XX and XY karyotypes in their blood cells. The exchange of blood cells alone is insufficient to cause freemartinism, since freemartinism does not occur in other species where anastomosis of placental vessels allows for chimaerism (*17*).

Cysts In and Around the Ovary

A variety of cysts that occur in and around the ovary have been described, but only cysts that occur within

the ovarian parenchyma will be described here. Cysts occurring within the ovary include follicular cysts, luteal cysts (luteinized follicular cyst), cystic corpora lutea, cystic rete ovarii, inclusion cysts derived from the surface epithelium, and cysts of the subsurface epithelial structures.

Luteal and follicular cysts are derived from anovulatory Graafian follicles and probably represent different manifestations of the same condition. They are most common in the cow and the sow, although they do occur in other species, and usually interfere with normal reproductive function in nonpregnant animals (*8,18–20*). In cattle, follicular cysts are most commonly encountered in heavily producing animals and in the winter months. There is evidence of genetic predisposition to cyst formation in the cow, but not in the sow.

The pathogenesis of follicular cyst formation is poorly understood, but it has been proposed that cystic follicles occur because there is insufficient release of luteinizing hormone (LH) to induce ovulation and luteinization of affected follicles. This hypothesis is supported by the response of affected animals to LH or gonadotropin-releasing hormone therapy and by the lack of degranulation of appropriate cells in the adenohypophysis of cattle with follicular cysts. Why some animals do not release sufficient LH to cause ovulation is uncertain. The amount of progesterone and estrogen secreted by anovulatory Graafian follicles varies considerably between individual affected animals, but normal cycling invariably ceases. Affected animals may exhibit signs of persistent estrus, nymphomania, or anestrus. Sows and cows with anovulatory ovarian cysts are usually anestrous. Reproductive behavior, at least in the cow, appears unrelated to blood levels of estrogen, progesterone, and testosterone (*18–22*).

In addition to effects on ovarian function in nonpregnant animals, hormones released from anovulatory follicles can induce changes in other tissues. For example, cows with follicular cysts may exhibit cystic endometrial hyperplasia or hydrometra, changes attributed to prolonged estrogenic stimulation (*8*). Conversely, follicular cysts are not common in the bitch and are not associated with cystic endometrial hyperplasia (*3*). In fact, most cases of cystic endometrial hyperplasia in the bitch occur during metestrus, when corpora lutea are present and the endometrium is largely stimulated by progesterone (*2*). Cystic follicular degeneration has not been shown to occur in the mare (*12*).

Anovulatory follicles continue to enlarge, so cystic follicles are, at least initially, larger than normal tertiary follicles (i.e., greater than 10 mm in diameter in the sow and 20 mm in the cow). Follicular cysts in the sow are frequently multiple and usually have areas of luteinization in the wall. The thickness of the granulosa cell layer that forms the lining of follicular cysts varies considerably between cysts, as does the extent of luteinization of the theca and granulosa cell layers. Luteinization is far more extensive in luteal cysts than it is in follicular cysts; however, not accurately defined as yet is the degree of luteinization of a follicular cyst that must occur to justify designation as a luteal cyst. In both types of cysts, an ovum is not usually found in the antrum (*8*).

Cystic corpora lutea are merely normal corpora lutea with a central cavity and do not cause functional problems. They are distinguished from anovulatory follicular cysts because they derive from follicles from which ovulation has occurred and therefore have an ovulation papilla. Luteal cysts have sometimes been mistakenly termed cystic corpora lutea. Cystic corpora lutea apparently produce sufficient progesterone in pregnant animals to maintain pregnancy (*19*). They occur in a variety of animal species.

Cysts of the surface epithelium occur relatively commonly in the mare and bitch. In the bitch, they usually derive from the subsurface epithelial structures (*3*). In the mare, cysts of the surface epithelium may become extensive and interfere with reproductive function. Cysts of the surface epithelium and subsurface epithelial structures are often multiple and remain confined to the ovarian cortex. The cysts are lined by cuboidal epithelium (*23*).

Cystic rete ovarii are most common in the bitch and the queen. The rete ovarii are normally located in the hilus of the ovary. Cystic rete ovarii appear as dilated epithelial-lined tubules, which can become so large as to compress the cortex of the affected ovary (*23,24*).

Persistence of the Corpus Luteum

Abnormal persistence of the corpus luteum occurs in several species. In the queen, and especially in the bitch, the corpus luteum is normally retained for a prolonged period after ovulation (*1*). In other species, retention of the corpus luteum in undesirable, as it frequently prevents normal cycling. Retention of the corpus luteum in cattle usually occurs postpartum in association with uterine disorders, such as fetal mummification, endometritis, pyometra, or hydrometra. Such disorders apparently disrupt normal cyclic luteolysis, perhaps because of impaired transfer of prostaglandin $F_2\alpha$ from the uterus to the ovary (*25,26*). In the mare, retention of the corpus luteum can occur spontaneously and in the absence of uterine disorders. Affected mares cease cycling (*12,13*).

The advent of the use of prostaglandins in veterinary medical practice has revolutionized estrous synchronization in cattle. To facilitate estrous synchronization in the past, corpora lutea were often manually enucleated, an undesirable procedure that often leads to extensive hemorrhage from the ovary.

Infectious Diseases

Vertically transmitted infectious agents, usually viruses, are transmitted in the germ cells; however, they will not be included in this discussion. Infectious diseases that involve the ovaries of domestic animals are apparently uncommon.

The infectious bovine rhinotracheitis virus infection

of cattle can cause lesions in the corpus luteum, and affected animals may produce less progesterone as a consequence (*27*). Porcine parvovirus can also cause lesions in the corpora lutea of infected pigs (*28*).

Granulomatous oophoritis can occur in animals that have either tuberculosis or brucellosis, although the incidence of these two diseases has now been greatly reduced in many countries. Pyogenic infections of the ovary and its surrounding tissues occur sporadically in cattle and swine; *Corynebacterium pyogenes* is invariably the culprit. Salphingitis can lead to extensive adhesions forming between the ovary and oviducts (*8*).

Ovarian Tumors

Tumors of the ovary have been described in all the domestic species, although they are relatively uncommon. Data on the incidence of animal tumors must always be interpreted in light of the fate of the domestic species, as only dogs, cats, and horses are usually allowed to live out their life expectancy. The relative youth of most food animals at time of slaughter obviously diminishes their prospects of developing neoplasms. Furthermore, ovaries are often not routinely examined, so small tumors could readily be overlooked.

Classification of primary ovarian tumors assumes that these tumors arise from one of three ovarian components: epithelium, either of the ovarian surface or rete ovarii; germ cells or; ovarian stroma, including the sex cords, which probably contribute cells to ovarian follicles and thus to the endocrine apparatus of the ovary. There are also tumors that defy categorization (*23,29*).

Epithelial Tumors. Epithelial tumors are uncommon in all domestic animals, with the possible exception of the bitch; however, they have been described in the mare, sow, queen, and cow (*23,29–31*). The vast majority of epithelial tumors arise from the surface epithelium, although rarely, they arise from the rete ovarii. In the bitch, these tumors arise most frequently from the subsurface epithelial structures, which are themselves derived from the surface epithelium. Hyperplasia of the subsurface epithelial structures is very common in older bitches, and distinction between hyperplasia and adenoma may be difficult (*3*). Epithelial tumors of the ovary have been induced in bitches given diethylstilbesterol for prolonged periods, and these estrogen-induced tumors regressed following withdrawal of hormone treatment (*32*).

Classification of epithelial ovarian tumors in animals is relatively simple, as carcinomas are not subdivided as they are in women. This may indicate either that sufficient difference in biological behavior of subtypes has not been observed in domestic animals, or more likely, that insufficient numbers of animals have been recognized with different tumor subtypes to generate reliable data on the biological behavior of the tumor. The veterinary pathologist is then concerned only with distinguishing benign and malignant forms.

Epithelial tumors of the ovary are usually cystic and papillary, thus, the names cystadenoma and cystadenocarcinoma are frequently used. Clear or yellow/brown fluid is present in many cysts. Solid areas are also present in most tumors. Histologically, these tumors consist of arboriform papillae that project into the cyst lumen. The papillae consist of a connective tissue stalk that is lined by single or multiple layers of cuboidal or columnar epithelial cells that may or may not be ciliated. The wall of the cyst typically is also lined by epithelium, and the lumen of the cyst may contain proteinaceous material. In the absence of metastasis or obvious vascular invasion, malignant tumors are distinguished from benign adenomas by the presence of stromal invasion in the former type. The cyst wall, the connective tissue papillae, or the stroma of the adjacent ovary may be invaded. Metastasis of carcinomas tends to occur transcoelomically, after rupture of cysts or invasion of the tumor, through the capsule of the ovary and subsequent implantation in the abdominal cavity (*23,29*).

Sex Cord-Stromal Tumors. Sex cord-stromal tumors are derived from, or histologically resemble, the normal cellular constituents of the ovary other than epithelium or germ cells. Included in this group of tumors are neoplasms with a diverse array of histological appearance that have been given an equally diverse, and confusing, array of names. A characteristic of these tumors is the coexistence of multiple cell types in the same tumor. The term "sex cord-stromal" reflects the uncertainty of the embryologic and histogenic origin of cells in these tumors (*23,29,33*). While it is generally accepted that ovarian stromal cells, specifically the thecal cells and their luteinized derivatives, arise from the mesenchyme of the primitive gonad, the origin of the follicular granulosa is more conjectural. Current information strongly suggests that the sex cords derived from the mesonephros (via the rete ovarii) are critical for follicle formation in the developing ovary of at least some species (*34–36*), however, the contribution of the surface (coelomic) epithelium to follicle formation is less established. Differences in activity of the surface epithelium in the developing ovary of different species suggests that the relative contributions of these two cell sources to primary follicle formation may be species dependent (*37*).

Given the uncertainties of embryologic origin of intrinsic ovarian stromal cells, their ability to assume different morphologic appearances in the normal ovary, and the possible cellular origin of these tumors [stroma, follicles, sex cords, interstitial glands, and undifferentiated rest cells (*29*)], the use of the term "sex cord-stromal tumors" is appropriate. The tumors in this group are designated as granulosa cell tumors, luteomas, thecomas, Sertoli cell tumors of the ovary, Leydig cell tumors, androblastoma, arrhenoblastoma, or lipid cell tumors. The appropriateness of some of these terms must be considered conjectural at best, and the term "sex cord-stromal tumor" is preferable.

Sex cord-stromal tumors share the potential to be hormonally active and to secrete steroid hormones. Unfortunately, these tumors are not readily classified on the basis of their endocrine products, as the types and amounts of different hormones secreted by different

tumors varies considerably. Given the similar structure of steroid sex hormones, and the demonstrated ability of thecal cells to produce androgens (*38*), it is not surprising that ovarian stromal tumors are capable of producing a diverse mixture of male and female sex hormones. The endocrine output from such tumors is often reflected in the behavior of the afflicted animal, typically varying from prolonged anestrus to nymphomania or masculinization (*8,23,29*). Hormones produced by these tumors can also induce changes in extraovarian tissues, especially in the tubular genital tract.

With the probable exception of the sow, sex cord-stromal tumors are the most common form of ovarian neoplasm in all species. In the bitch, sex cord-stromal tumors and tumors of the subsurface epithelial structures have a similar incidence.

Stromal tumors of the mare's ovary are usually classified as granulosa cell tumors, or granulosa-theca cell tumors (*8,29,39–42*). The latter term reflects the usual coexistence of cells interpreted as granulosa cells and theca cells. A single tumor of a similar type has been reported as an arrhenoblastoma (*43*). Sex cord-stromal tumors typically are polycystic and histologically are seen to consist of cysts that resemble disorganized attempts at follicle formation, accompanied by a prominent supporting stroma of spindle cells interpreted as theca cells. Within the follicular structures are multiple layers of cells that resemble granulosa cells, often with palisading at the periphery. In other tumors, the follicular pattern is less apparent, and neoplastic cells are arranged in cords and nests. This latter type of stromal tumor has been termed Sertoli cell tumor of the ovary.

Recently, different endocrine abnormalities were detected in mares with different patterns of sex cord-stromal cell tumors (*41*). Mares with the Sertoli pattern had elevated levels of estrogen, but not androgen, whereas mares with the more typical granulosa cell pattern and Leydig-like cells in the interstitium invariably had elevated androgen levels and varying degrees of masculinization. The investigators noted a correlation between number of Leydig-like cells and blood androgen levels and speculated that the source of the androgen might be the Leydig-like cells. An alternative is that these cells in fact represent early attempts at luteinization of granulosa or theca cells in the neoplastic follicles. Mares with sex cord-stromal cell tumors may be apparently normal or exhibit stallion-like behavior and masculinization, nymphomania, or anestrus.

In the bitch, a variety of patterns of stromal tumor have been reported, including granulosa cell tumors, Sertoli cell tumors, luteomas, and nonspecific stromal tumors (*3,23,29,44,45*). Differences in metastatic potential in these variants suggest subdivision is warranted (*45*). Interestingly, the so-called Sertoli pattern of stromal tumor is very similar to the appearance of the granulosa cell cords present in the normal canine ovary. As in other species, these tumors can be hormonally active and induce changes of hyperestrinism (*44–46*).

Stromal tumors are the most common primary ovarian tumor in the queen, and tumor types described include granulosa cell tumors, luteomas (including lipid cell tumor), and androblastomas (Sertoli-Leydig pattern) (*23,29,31,47,48*). Luteomas, or lipid cell tumors, of the cat are composed of cells that resemble those found in the interstitial glands. Granulosa cell tumors often have a microfollicular pattern and are the predominant type of ovarian tumor in the queen. Metastasis of sex cord-stromal tumors is probably more common in the queen that it is in the bitch. Signs of hyperestrinism may accompany these tumors.

In the cow, sex cord-stromal tumors are usually granulosa-cell or Sertoli-cell type (*23,29,49,50*). Thecomas and luteomas have also been recognized (*23*). Affected cattle may exhibit masculinization, nymphomania, or be asymptomatic.

Although described in the sow (*51*), sex cord-stromal tumors are apparently uncommon. This probably reflects the rather short life expectancy of swine in today's intensive production systems.

Germ Cell Tumors. Germ cells are initially found in the yolk sac and, early in differentiation, migrate to the gonadal ridge. In the developing ovary, association of germ cells and sex cords leads to the formation of primary follicles. Dysgerminomas and teratomas are derived from germ cells and both occur in domestic animals (*23,29*). Other germ cell tumors that occur in women, such as embryonal carcinoma and choriocarcinoma, have yet to be described in animals.

Dysgerminomas are considered to be the female equivalent of seminoma of the testicle. This is a rare ovarian tumor in domestic animals, but it has been reported in most species and is most common in the bitch and the queen (*23,29,52–54*). Dysgerminomas are highly cellular tumors, consisting of broad sheets, cords, and nests of cells separated by connective tissue septae. Individual cells are large, polyhedral, with vesicular nuclei and prominent nucleoli. Multinucleate cells and focal aggregations of lymphocytes may be present. Metastasis can occur. Hypertrophic osteopathy has been described in mares with dysgerminomas (*55,56*).

Teratomas are composed of tissue derived from at least two, and often all three, germinal layers. Presumably, they arise from pluripotential stem cells. Ovarian teratomas are also uncommon in the domestic animals, but have been described in most species (*23,29,53,54*). They typically have solid and cystic areas, the latter often containing sebaceous material and hair. A variety of other tissue types may be present, including bone and teeth. Malignant teratomas have been described, particularly in the bitch (*54*).

Miscellaneous Tumors. A single gonadoblastoma has been described in the testicle of a dog (*57*). This tumor can occur in either human males or females, so if the canine equivalent does exist, it could occur in the ovary. Gonadoblastoma contains both germ cells and sex cord-stromal cells.

Mesenchymal Tumors. The ovary is not immune to development of tumors of its mesenchymal element, including fibromas, hemangiomas, leiomyomas, and their malignant counterparts (*23*). Such tumors are not com-

mon, except ovarian hemangiomas of the sow. These tumors are common in older sows and are proposed to arise in the corpora lutea (*58*). Hemangiomas must be distinguished from vascular hamartomas that occur in the ovaries of some species.

Metastatic Tumors. Secondary tumors are not uncommon in domestic animals, as lymphosarcomas can occur at this site in the bitch, sow, queen, and cow (*8*). Other tumors are less common.

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