Pathology of the Female Reproductive System

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Uterine Cancer in Zoo Cats from Hormonal implants

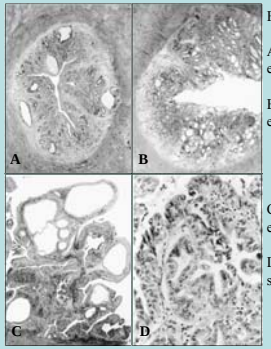
Introduction

Domestic cat owners do not typically think of hormone-based birth control when preventing their pet from having offspring. However, in an environment such as a zoo, reproductive management of threatened or endangered zoo-maintained felids requires safe and reversible contraception. One common method of contraception is the use of melengestrol acetate (MGA) in the form of an implant, which is effective in preventing pregnancy; however, long-term use has been associated with endometrial hyperplasia, endometrial cancer, and mammary cancer.



The Implant

Progestin, a natural or synthetic steroid hormone, promotes endometrial growth and secretion, and smooth muscle relaxation in the uterus. Thus, progestin-induced contraception is thought to work via inhibiting uterine motility and decreasing endometrial receptivity. MGA, a steroidal progestin, is administered in a silastic implant, and when placed subcutaneously or intramuscularly, provides extended release of a potent progestin that prevents reproduction.



Endometrium, Lion.

A.) Mild (grade 1) endometrial hyperplasia

B.) Moderate (grade 2) endometrial hyperplasia

C.) Severe (grade 3) endometrial hyperplasia

D.) Cellular atypia, severe hyperplasia

Clinical Signs

- Anorexia
- Purulent discharge
- Rear limb weakness
- Hard mass when palpating lower abdomen

Clinicopathological Findings

- Endometrial hyperplasia
- Endometrial mineralization
- Hydrometra
- Endometrial cancer
- Leiomyosarcoma
- Mammary cancer

Conclusions

MGA is an effective means of providing contraception to zoo felids, however it is not without consequences, which may be severe. Recently, other contraceptives have been investigated in zoo animals, including Suprelorin®, with promising results; however it is associated with significantly prolonged time to return to estrus.

Human Connections

While MGA is not approved as a human contraceptive, similar conditions can result from the manipulation of reproductive hormones. Doctors have found that using estrogen alone can lead to endometrial cancer in women. Progesterone-like drugs must be given along with estrogen to reduce the increased risk of endometrial cancer. This approach is called combination hormone therapy.

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Mammary Gland Cancer in Dogs

Introduction

Mammary gland cancer is the most common type of tumor in unspayed dogs. The risk of developing cancer increases as a dog ages without being spayed, which is thought be correlated with the hormones of the estrous cycle. There is a 0.5% risk if spayed before 1st heat, 8.0% if spayed after 1st heat, and 26.0% if spayed after 2nd heat. The median age of cancer development is 10.5 years.

Risk Factors

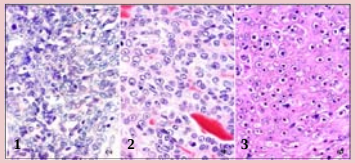
- Delayed spaying
- Red meat consumption
- Mutations to BRCA1 and BRCA2 tumor suppressor genes
- Obesity
- High fat diet

Tumor Development

Types of Masses

- Benign mixed tumors
- Hyperplasia
- Adenomas
- Malignant mixed tumors
- Sarcomas
- Various carcinomas

Once a tumor has developed in the mammary gland and if left untreated, it will likely metastasize to the lymph nodes and lungs, and has potential to spread to the skeleton. In gross appearance, the tumor is a proliferation of nodules varying in size that are usually firm and grayish in color. The caudal glands are involved more often than cranial ones, possibly because caudal glands retain secretory potential longer, which induces glandular growth.



From left to right:

1. Complex carcinoma, low severity.
2. Solid carcinoma, malignant mixed tumors, medium severity.
3. Adenosquamous carcinoma, severe.

Clinical Signs

- Anorexia and/or weight loss
- Formation of superficial masses in mid- and caudal abdomen; detectable masses at superficial lymph nodes
- Pain around mammary glands and limbs(common with inflammatory carcinoma)

Treatment

- Lumpectomy (surgical removal)
- Simple mastectomy (removal of affected gland and those sharing lymph nodes)
- Radical mastectomy (removal of all mammary glands and associated lymph nodes)

Human Connections

In comparison to human breast cancer, there is similar pathogenesis as the *BRCA1* and *BRCA2* mutations are implicated in both. There is a similar age of onset (median age of 58 in humans is equivalent to dog age 10.5). Treatment is similar and depending on stage, surgical intervention is the most common treatment. Breast cancer is often hereditary in humans; this does not seem to be true in dogs, although some breeds appear to have predisposition.

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Endometriosis in Non-human Primates

Introduction

Endometriosis is one of the most common reproductive disorders in Old World nonhuman primates. Due to the high occurrence rate of the disease and similarity to human anatomy, the nonhuman primate has been proposed as a naturally occurring model of this disease in humans, and the condition has been induced experimentally in macaques and baboons through endometrial autografts to the peritoneal cavity.



The Disease

Endometriosis is defined as the presence of both endometrial glands and stroma outside the uterine cavity and musculature. Exposure to ovarian hormones is required for the development of disease, which grows gradually as the female matures. Clinical studies indicate that retrograde menstruation is the probable mechanism by which endometriosis occurs. Risk factors include frequent X-rays, ovarian steroids, and uterine surgery that may seed the abdomen with endometrial tissue.

Clinical Signs

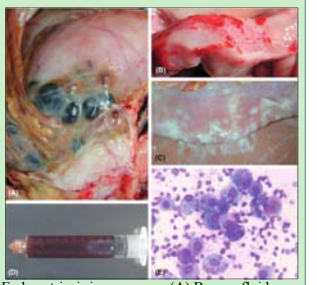
- May be asymptomatic
- Pain and failure to conceive
- Cyclical anorexia, weight loss, depression
- Absence of feces for several days
- Abdominal distention
- Large mass upon palpation of lower abdomen.

Diagnosis Techniques

- Serum/peritoneal fluid testing (CA-125)
- Imaging techniques (US and MRI)
- Surgical examination of peritoneal cavity
- Cytology of peritoneal fluid consistent with endometriosis

Treatment

- Hysterectomy (surgical removal)
- Danazol, drug promoting chronic anovulation with hyperandrogenism
- Progestational agents that promote decidualization of endometrial tissue, then eventual atrophy



Endometriosis in macaques. (A) Brown, fluid-filled, cysts producing adhesions between uterus and colon. (B) Multifocal, plaque-like, vivid red lesions on surface of the colon. (C) Cystic and fibrotic lesions between liver and diaphragm. (D) Typical dark red-brown viscous gross appearance of endometriotic fluid. (E) Typical cytologic appearance of endometriotic fluid

Human Connections

In women and baboons with severe endometriosis, aberrant *HOXA10* expression was associated with hypermethylation of the *HOXA10* gene, indicating that the disease may be due to post-transcriptional modifications as a method of gene silencing or activation. The baboon model is an important model for exploring therapeutic targets for reducing disease development and improving pregnancy success rates. Another finding indicates that the inflammatory cytokine TNF-α is a potent modulator of the inflammatory process and has been shown to be elevated in the peritoneal fluid of women with endometriosis.

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Slide 1

1 uterine motility:

sperm or fertilized zygote?
Liana Yates, 3/7/2014