Reproductive challenges in small mammals

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The objective of this presentation is to briefly describe normal reproductive structures and function in small mammal species, and primarily focus on clinical diagnosis and management of common reproductive disorders with an emphasis on pet species of rodents (rats, guinea pigs, gerbils, chinchillas, hamsters, degus), rabbits, hedgehogs, sugar gliders, and ferrets.

Rabbits

There are several unique features of rabbit reproductive anatomy and physiology worth addressing. In the female, the paired ovaries are connected to paired oviducts, which connect to the long, well-vascularized, and slightly convoluted uterine horns.[1,2] The uterine horns each have their own cervix, which separates the uterus from the vagina. The rabbit vaginal vestibule is relatively long, wide and flaccid compared to other mammals.[1] These unique features are important to understand, particularly when performing an ovariohysterectomy. In the male, the paired, scrotal testicles are elongated and more flaccid compared to many other mammals. The skin of the scrotum is relatively thin and wrinkled. The inguinal canals remain open after the testicles descend, whereas most male mammal inguinal canals constrict after testicular descension.[1,2] After castration, herniation of abdominal organs can occur through these open inguinal canals, so appropriate closure of underlying tissues should be a concern.

Rabbits are induced ovulators, and ovulation occurs approximately 10 hours after coitus. Wild rabbits have a seasonal pattern to reproduction, but pet rabbits will breed year-round if allowed.[1,2]

Sex determination can be somewhat challenging in rabbits. One needs to press down on either side of the external genital region in order to express the penis or vulva. The expressed penis is cylindrical in shape. The vulva also protrudes from the perineum and can easily be mistaken for a penis. Look for the vertical vulvar slit and two distinctive blood vessels visible running along each side of the vulvar protuberance into the vagina.[1]

Uterine neoplasia

Early elective ovariohysterectomy in female rabbits is relatively common, making uterine neoplasia much less common than 10 years ago. Uterine tumors are the most common reproductive tract neoplasms of older, intact female rabbits and the incidence increases dramatically with age.[1,2] Depending on the publication, greater than 75% of intact female rabbits will develop uterine tumors by 6-7 years of age.[1] Uterine adenocarcinoma is the most common of the uterine neoplasms. These tumors are slow to metastasize, but metastatic disease occurs, and can affect the lungs, liver, brain, and other organ systems. Other uterine tumors reported include adenoma, leiomyoma and leiomyosarcoma.[1,2] Diagnosis includes abdominal palpation to confirm suspicion of a mass affect, and imaging modalities (ultrasonography, CT or contrast CT scan) with biopsy and histology or fine needle aspiration and cytology. A contrast CT scan may also help identify metastatic disease, which will provide prognostic information, with metastatic disease being a poor to grave prognosis. Treatment of any uterine tumor relies on removing the affected uterus and ovaries via ovariohysterectomy.

Pyometra

Pyometra is uncommon in pet female rabbits, but occurs more commonly in females maintained for breeding.[1] Typical clinical signs include a rabbit with a depressed attitude, a mucopurulent vulvar discharge, and a palpably enlarged uterus. Sepsis can occur with chronicity. Imaging (ultrasonography or CT scan), in addition to a vulvar swab with cytology, will help with diagnosis. Treatment includes ovariohysterectomy, bacterial culture and sensitivity of the intrauterine material, and broad-spectrum antibiotics.

Dystocia

Dystocia is uncommon in rabbits, but is reported in the literature. Gestation ranges from 28-36 days in length.[1,2] Dystocia may be more common in rabbits that are obese, produce larger fetuses, have a narrower pelvis, or experience uterine inertia.[1,2] Pregnant rabbits in dystocia may be presented with a history of straining, depressed attitude, vaginal discharge, and passage of some fetuses. Imaging (ultrasonography and radiographs) will help to characterize the presence of remaining fetal skeletons. Medical treatment includes fluid therapy, sedation, analgesics, oxytocin (1-3 iu/rabbit, subcutaneously), and gentle removal of the fetuses and fetal membranes.[1] However, cesarian section is typically indicated, and may include ovariohysterectomy after removal of any viable fetuses.

Cryptorchidism

Cryptorchidism refers to the failure of one or both testicles to fully descend into the scrotum. Testicular descent occurs by approximately 12 weeks of age in male rabbits.[1] With cryptorchidism, the testicle or testicles may remain in the caudal abdomen or within the proximal inguinal canal. A word of caution; during normal handling and physical examination, males with descended testicles, commonly retract their testicles temporarily into the inguinal canal making it appear that the testicles are not descended. Sedation will relax the rabbit and allow proper assessment of testicular descent. Ultrasonography may help identify whether the testicles are intra-abdominal versus within the proximal inguinal canal. As with other mammals, cryptorchidism may lead to an increased incidence of testicular neoplasia. Castration via the inguinal canal or via an intra-abdominal approach is indicated in these cases.

Testicular tumors

Testicular tumors tend to occur in older, intact males and are not commonly observed in pet rabbits, as many are neutered earlier in life. Sertoli cell tumors, seminomas, interstitial cell tumors and gonadoblastoma are reported.[1,2] Surgical removal of the affected testicle is the treatment of choice, and removal of the unaffected testicle at the same time is recommended.

Treponematosis

Treponema paraluiscuniculi ("rabbit syphilis") is a spirochete that can affect both male and female rabbits, and is most common in intact rabbits as the organism is commonly transmitted through sexual contact.[1,2] Vertical transmission of *Treponema* from dam to the fetus can occur during vaginal passage during parturition.[1] Clinical signs include ulcerative, crusty, or vesicular lesions associated with the mucocutaneous junctions of the mouth, eyes, nose, and genitals. Diagnosis is based on appearance of lesions, and silver staining of skin scrapes or biopsy specimens of the lesions.[1] Serology is also available at some commercial laboratories with submission of plasma samples. Penicillin procaine with benzathine is most commonly used for treating treponematosis, but any penicillin must be administered subcutaneously and not orally in rabbits.

Hypersexuality and hyperaggression

Hypersexuality and hyperaggression occasionally occurs in male and female rabbits, even after castration/ovariohysterectomy. This behavior may be associated with a hormone secreting tumor, or without an obvious cause.[1] Behaviors include excessive mounting, biting, fighting, and urinating. Imaging (CT scan or ultrasonograpgy) is recommended in order to rule out endocrine or other organ system tumors. A contrast CT scan may be helpful in ruling out pituitary tumors. Surgery should be considered if a discrete tumor can be identified and removed. Gonadotropin releasing hormone (GnRH) agonists, such as deslorelin implants, may be implanted to try to decrease the behavior by reducing reproductive hormones.[3,4] Euthanasia is not uncommon with hyperaggressive rabbits, as owners are not able to deal with, or provide appropriate care for these rabbits.

Rodents

For the purpose of these proceedings, "rodent" refers to the following: rats, guinea pigs, chinchillas, gerbils, hamsters and degus. Reproductive disorders of rodents are common and are predominantly neoplastic diseases.

In all species listed, females have bilateral ovaries and a bicornuate uterus, consisting of two uterine horns, a uterine body, a cervix and a vagina, except for the rat, in which the two uterine horns join together and open into the vagina.[5-8] Males have two scrotal testicles, and open inguinal canals, much like rabbits. All have a penis and a prepuce, and rats have an os penis. Mammary tissues are extensive in many rodents of both sexes, particularly in rats and mice, which is important in some disease processes. Determining sex is relatively straightforward in most rodent species, with anogenital distance larger in males than in females. As with rabbits, sex determination in young animals can be more challenging.

Ovarian cysts

Ovarian cysts, or cystic rete ovarii, are common in guinea pigs, gerbils, and some hamster species, however, the etiology is unknown. Prevalence in guinea pigs increases with age and ranges from 30-90% depending on which publication one reads. Middle-aged (2- to 4-year-old) sows are most commonly affected.[6-8] Definitive underlying mechanisms associated with reproductive history and cyst development have not been determined. Concurrent diseases associated with ovarian cysts include leiomyomas, granulosa cell tumors, cystic endometrial hyperplasia, and endometritis.[6-8] Clinical signs may include abdominal distension, nonpruritic bilateral alopecia especially of the flanks (functional follicular cysts), lethargy, and anorexia. Frequently, the cystic structures are palpable during a physical examination, but overzealous palpation can cause rupture of the cyst. Diagnostics include imaging (e.g., ultrasonography) to visualize the cysts; pancytopenia may be observed secondary to hyperestrogenism on a complete blood count, but cystic ovaries do not always produce excessive estrogens. The current treatment of choice is surgical ovariohysterectomy. There is interest in GnRH agonists, but a single published study found no effect on cystic ovaries in guinea pigs administered deslorelin implants.[8] Future research with GnRH agonists will be beneficial.[9]

Female reproductive neoplasia

Uterine tumors. Uterine tumors are common in female rodents with malignancy diagnosed most frequently in hamsters and gerbils, and benign uterine tumors more common in rats.[5,6] Benign endometrial stromal tumors are most common in older female rats, with sarcomas most common in mice, and adenocarcinomas in hamsters and gerbils. In guinea pigs, uterine tumors include leiomyomas and leiomyosarcomas. Approximately 50% of these guinea pig uterine tumors are malignant, but metastasis is not common.[7,8] Clinical signs in all rodents include hemorrhagic vaginal discharge, abdominal distention, and abdominal pain.[5,6] Imaging (CT scan and ultrasonography) may help with diagnosis and for evaluating the animal for metastatic disease. Fine needle aspirate of uterine masses may provide a cytologic diagnosis. The treatment of choice is ovariohysterectomy with histopathologic evaluation. Prevention of all reproductive neoplasms is best accomplished by ovariohysterectomy of young animals.

Ovarian tumors. Ovarian tumors are most common in rats, and most of these are diagnosed as tubular ovarian adenomas.[5,6] Other ovarian tumors diagnosed in rodents include granulosa cell tumors, thecal cell tumors, malignant granulosa cell tumors, ovarian mesotheliomas, tubular adenocarcinomas, and papillary cystadenomas/cystadenocarcinomas.[5-8] Imaging (CT scan and ultrasonography) may help with diagnosis and for evaluating the animal for metastatic disease. Ovariohysterectomy is the treatment of choice, but the prognosis will be poor if the tumor is malignant or if metastatic disease is present.

Mammary gland neoplasia. Mammary gland neoplasia is particularly common in rats and mice. Malignant mammary adenocarcinoma and fibrosarcomas are most common in mice, while benign mammary fibroadenomas are very common in rats and guinea pigs of both sexes; adenocarcinomas also occur in rats and guinea pigs.[5-8] Mammary tumors are not common in most hamster species, but Djungarian hamsters have a higher prevalence of mammary tumors than other hamster species.[6] In rats, mammary tumors can occur almost anywhere on the body, as mammary tissue is diffuse and extensive. In

female rats, there is evidence that ovariohysterectomy early in life (between 3-6 months of age) will protect the rat from developing mammary tumors as the rat ages.[5,6] There is anecdotal evidence that ovariohysterectomy at the time of first mammary tumor surgical removal, may reduce or delay recurrence of the mammary tumor, but there are no systematically derived data supporting this hypothesis. Fine needle aspirate of mammary masses may provide a cytologic diagnosis. Surgical excision is the treatment of choice for mammary tumors in any species, but recurrence is common, and in those rodent species in which malignant tumors are excised, the prognosis is poor. Surgical excision can be very difficult depending on location of the tumor(s); inguinal and perineal masses can be particularly problematic due to close proximity to other vital structures. Many benign fibroadenomas are well-vascularized, so care should be taken during surgery to minimize hemorrhage. Dehiscence of the surgical site is common in guinea pigs, partially due to the fact that their immune system reacts dramatically to foreign suture material. More recently, subcutaneous deslorelin implants have been administered in rats after surgical excision of mammary tumors, with the hope of delaying recurrence without putting the rat through an invasive ovariohysterectomy. Our service is monitoring efficacy of this approach, but we have not collected enough data at this time.

Pregnancy toxemia

Pregnancy toxemia is most commonly observed in guinea pigs either just before or just after parturition.[7,8] There are two forms of pregnancy toxemia. The first is metabolic toxemia with ketosis occurs late in pregnancy and early postpartum, which may be associated with stress and starvation (negative energy balance). Predisposing factors include obesity, lack of exercise, large fetal loads, change in diet and/or environment, heat stress, and primiparity.[7,8] Clinical signs include anorexia, dehydration, and with chronicity, ataxia, dyspnea and death. Breath can smell like ketones with ketonemia. Diagnostic testing includes a blood sample (hypoglycemia), urinalysis (ketonuria), and imaging (CT scan and/or ultrasonography).[7,8] Treatment will include force-feeding, and fluids with dextrose, but the prognosis is poor. The second form of pregnancy toxemia is vascular compromise associated with the uterus compressing its own vascular supply or that of the kidneys or gastrointestinal tract, leading to tissue ischemia and hypertension.[7,8] This is equivalent to preeclampsia in women and occurs in late pregnancy. Diagnosis includes indirect blood pressure to confirm hypertension, and ultrasonography with Doppler to evaluate blood flow. Treatment includes fluid therapy, analgesics and cesarian section, with a poor prognosis. With a poor prognosis for both forms or pregnancy toxemia, prevention is critical and includes decreased stress and good nutrition during pregnancy, and encouraging exercise.

Dystocia

Dystocia is more common in guinea pigs than other rodents or rabbits, and it has been attributed to large pups, narrow pelvic canals, or fusion of the pubic symphysis.[7,8] The pubic symphysis is a fibrocartilaginous bridge in female guinea pigs, which calcifies and is permanently fused if the female has not been bred by 5-6 months of age. Other contributing factors include obesity, hypovitaminosis C, and uterine inertia.[7,8] Sows at risk should be monitored and should undergo a cesarian section at the time of parturition.

Male reproductive neoplasia

Testicular tumors are reported in rodents. In rats, testicular interstitial cell tumors (Leydig cell tumors) are most common.[5,6] Other tumors documented in mice, guinea pigs, hamsters, gerbils and chinchillas include seminomas, epididymal adenoma/adenocarcinoma, amongst others.[5-8] Surgical orchiectomy is the treatment of choice for testicular tumors in any rodent species.

Fur ring and paraphimosis

Fur ring and paraphimosis are most common in male chinchillas.[9] Fur ring is characterized by fur encircling the glans penis. Smegma can also accumulate in this same penile region causing adhesion of the prepuce to the glans penis.[9] Clinical signs may include excessive grooming of the prepuce, straining to

urinate or chronic exposure of the glans penis (paraphimosis). Balanoposthitis, or infection of the prepuce and glans penis can occur, causing the same clinical signs. In severe cases, ability to urinate is compromised and the condition becomes emergent. Treatment includes removing any fur or smegma from the prepuce and penis using cotton tipped applicators and an antimicrobial solution (dilute chlorhexidine).[9] Topical antimicrobial ointments can be applied to the affected area locally, and systemic antibiotics and non-steroidal anti-inflammatories can be administered.

Ferrets

The female reproductive tract is similar to the cat, with paired ovaries, uterine horns, a short uterine body and a single cervix.[11] Females are induced ovulators, and the vulva swells during estrus. Males have a small prepuce and a palpable os penis. Once descended, the testicles are contained in a scrotum.

Many diseases of the reproductive tract that occur in other small mammals, do not occur in most pet ferrets, since early ovariohysterectomy and castration (≤ 6 weeks of age) is extremely common prior to sale in the United States. In European countries, however, intact ferrets are more common and early spay and neutering is much less common. Deslorelin implants can be an effective alternative to surgical castration in intact ferrets.[12] Some common neoplastic diseases of the endocrine system produce reproductive hormones, which cause prostatomegaly, aggressive and reproductive behavior in males and vulvar enlargement in females, but these are considered independent of true reproductive diseases. Because most pet ferrets in the United States are spayed and neutered early in life, most commonly, neoplastic diseases are diagnosed.

Female reproductive diseases

Female reproductive diseases most commonly include neoplastic diseases.[11,13] In intact females, ovarian tumors are most common, but uterine tumors also occur. Metastatic disease associated with ovarian or uterine tumors is not reported in the literature, so ovariohysterectomy is the treatment of choice with any female reproductive tract neoplastic disease.[11,13] Mammary tumors in female ferrets are rare and have been reported as benign and malignant.[11,13] Surgical excision, much like dogs and cats, to include the affected mammary chain, is recommended.

Male reproductive diseases

Male reproductive diseases most commonly include preputial tumors, but intact males may develop testicular tumors, cryptorchidism, and primary prostatic diseases.[11,13] Preputial adenomas and adenocarcinomas (apocrine gland tumors) have been diagnosed and can occur in castrated males as well as intact males. Most preputial gland tumors are malignant and infiltrate local tissues, as well as metastasize to lymph nodes and lungs.[11] Clinical signs include raised masses of varying color associated with the prepuce. Overgrooming by the male may cause dermatitis or ulcerative lesions. Imaging (contrast CT scan) will help diagnose metastatic lesions providing prognostic information. Surgical removal is the treatment of choice, but this can be a complicated procedure due to the aggressive infiltration of the tumor into adjacent tissues.

Sugar gliders

Sugar gliders have become popular pets during the past ten years. They are nocturnal marsupials native to forests of Australia and New Guinea.[14] The "glider" name derives from the patagium used for gliding from tree branch to tree branch in the forest, that stretches from hind limbs to forelimbs. Sugar gliders have a cloaca where the gastrointestinal, urinary and reproductive tracts meet and exit.[14] Male sugar gliders can be distinguished from females by the presence of an oval-shaped scent gland on the top of the head and a ventral midline scent gland located near the thoracic inlet.[14] Females have a pouch in which young are raised, much like other marsupial species. Male anatomy is unique as the males have a bifurcated penis and two testicles contained in a pendulous scrotum located cranial to the cloaca on ventral midline. Males urinate from the base of the bifurcated penis, not the distal tip.[14] The female sugar

glider has two uterine horns, and two vaginas that end in a septate, sac-like structure. Reproduction is polygamous and seasonally polyestrus.[14]

Elective ovariohysterectomy is uncommonly performed in female sugar gliders due to the risk of hemorrhage in such small individuals, but castration of the males is common and an extremely simple procedure with the proper instruments.

Reproductive diseases

Mutilation of the penis, scrotum, cloaca and tail in males is the most common disease process of the sugar glider reproductive tract, and a condition that is poorly understood.[14,15] Hypotheses associated with the cause of this behavior include single housing or improper socialization, lack of access to females, and poor husbandry (inappropriate nutrition, not maintaining nocturnal environment). However, the cause remains unknown. Males will attack their organs, chewing them, and even eviscerating themselves. This is an emergency situation, and surgical repair or euthanasia are the options. If the injuries can be repaired and the glider survives, it is imperative that the animal does not have access to the same tissues once it recovers from anesthesia (use of E-collars and body coverings are necessary). If the tips of the penis are affected, the tissue can be surgically removed without consequences to urination, as the urethra exists at the penile base. With severe damage, the prognosis is grave and the euthanasia should be considered. There is some anecdotal information that castration may be preventative.

Orchidectomy

Orchidectomy is relatively simple using a CO_2 laser or a Ligasure® system. This will minimize post-surgical self-trauma compared to using scalpel and sutures.[15]

African hedgehogs

African pygmy hedgehogs are very popular pets. They are not rodents, but members of the insectivore Family, *Erinaceidae*.[16] African hedgehogs are nocturnal and native to the savannah regions of east and central Africa. They are smaller than European hedgehogs, and their integument is covered in spines, which are a deterrent to predators. If you are able to prevent a conscious hedgehog from rolling into a ball, sex determination is relatively easy. The male has a prominent prepuce and the penis is large and palpable. Two testicles are present in a para-anal sac, without a true scrotum.[16] The female has an obvious external vulva, a single vagina with two prominent uterine horns ending in a cervix without a uterine body. African hedgehogs are polyestrous and breed throughout the year in captivity.[16] Although not confirmed, African hedgehog females are thought to be induced ovulators.

Elective ovariohysterectomy and castration are less commonly performed in hedgehogs compared to other small mammals, but the prevalence of reproductive tract neoplasia makes therapeutic ovariohysterectomy common in older females. The most common reproductive diseases of African hedgehogs are neoplastic.

Uterine neoplasia

Uterine neoplasia is very common in in middle-age to older female hedgehogs, and malignancy is common.[16,17] In a survey of uterine tumors, most were reported in females 3-5-yeasr of age and included adenocarcinomas, endometrial stromal sarcomas, endometrial polyps, and adenoleiomyoma/adenoleiomyosarcoma. [17] All hedgehogs with uterine disease are presented with similar clinical signs; hematuria and weight loss. Imaging (CT scan and/or ultrasonography) is important to rule out reproductive versus urinary diseases, and to try to determine whether metastatic disease is present. Ovariohysterectomy is the treatment of choice for any female hedgehogs with uterine disease.

Mammary neoplasia

Mammary neoplasia is also common in female hedgehogs, and adenocarcinomas are most common.[16] These tumors can be invasive and grow large enough that many females are presented with ulcerative and necrotic lesions of the skin overlying the masses. Diagnosis includes fine needle aspirates

and cytology or biopsy and histopathology. Imaging may be useful for prognosis since metastatic lesions in lymph nodes and lungs are common. These tumors are well-vascularized, so hemostasis is critical when surgically excising the mass. Preventing access to the surgical wound is important in hedgehogs because many will obsessively lick and chew the wound until it dehisces.

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