Clinical approach to infertility in the cat

Aime Johnson
Auburn University College of Veterinary Medicine
Auburn, AL

Abstract

Causes of infertility in the cat are often multifactorial. Cattery management should be addressed prior to evaluation of individual animals. Factors such as housing/lighting, preventive care, and disease status of the colony should be evaluated. A complete physical examination is vital to rule in or out anatomical abnormalities leading to infertility. In the tom and queen, good breeding management is vital for success. In queens, infertility can be caused by persistent receptivity/estrous behavior, refusal of the male, and ovulation without pregnancy. When evaluating a tom, failure to mate or failure to achieve pregnancies are the most common categories. A detailed history and complete breeding soundness examination is important to differentiate and identify potential causes of infertility.

Keywords: Cat, infertility, queen, tom

Introduction

When confronted with a case of feline infertility, male or female, a complete history including vaccination and disease status is essential. Many issues can be contributed to improper management (see next section on history). A good general physical examination (observing for comorbidities that could affect reproduction) is performed next. Body condition of the cat, overall appearance, grooming, and attitude should be observed in both males and females. In the male, special attention should be placed on examining the mouth and gums. Mouth pain (e.g., gingivitis or tooth pain) can affect the ability of the male to bite the scruff of the female when mating and therefore hinder the breeding attempt. Any back or rear limb pain in the male can also affect the breeding process or his willingness to mate. An external reproductive examination should follow the general physical examination and will be discussed later for the female and male separately. Blood analyses (e.g., complete blood count, serum chemistry, and possibly hormonal testing) may be indicated depending on the findings of the physical and reproductive examinations. Ultrasonography should be performed to evaluate both testes in the male, and uterus and ovaries in the female. Sedation may be required depending on the cooperative behavior of the patient. If external or internal reproductive abnormalities are present, or if there is no other obvious cause for the infertility, a karyotype of one or both members of the breeding pair may be necessary to confirm whether the genetic makeup of the animal is normal.

History

Specific questions to gain a baseline knowledge of the cattery management include.[1]

- How many animals are housed in the facility (male and female, breeding and nonbreeding)?
- What are their ages?
- What is the source of each animal and how long has each been with the colony?
- What is the diet, water source, and preventative health policy?
- What is the supplemental lighting program?
- What is the current disinfection policy for floors, litterboxes, bowls, etc.?
- What is the procedure for bringing male and female together?
- What is the procedure for pregnancy confirmation?
- Where are pregnant queens housed during pregnancy, delivery, and lactation?
- What bedding or boxes are provided to the animals at each stage (breeding, pregnancy, queening, and lactation)?
- Is breeding or queening observed, or does it occur with no one present?
- How are kittens managed from birth to weaning?
- Can a detailed breeding and queening report for each animal be provided?
- What are the specific issues the cattery is experiencing?

Additional questions may be necessary depending on the answers received.

Cattery Management

Vaccination status of all animals in the colony or household should be evaluated to ensure adequate disease control. Although a closed colony is preferable with no new animals entering, such a policy may also limit the introduction of new genetics. A quarantine period with adequate testing procedures should be mandatory for all new additions. A quarantine process should also be in place for any cats that leave and return to the colony for breeding, exhibition, etc. Cats in different stages should be housed separately. Breeding animals, pregnant, and nursing mothers should be kept away from all other cats. Late pregnant and lactating mothers should be kept in a quiet comfortable space to reduce stress and minimize stress-induced cannibalization of their young.

In catteries, strict sanitation and adequate ventilation are essential to reduce or eliminate disease. Poor sanitation often leads to clinical signs of disease and neonatal mortality from sepsis. Standard operating procedures should be followed to prevent hygiene errors. Litter boxes, bedding, toys, food, and water bowls should be cleaned and disinfected regularly. Frequency will depend on the density of the cattery, but in general, cleaning should be performed daily with complete disinfectant done at least weekly. Caution is needed to ensure that the disinfectant used is at an appropriate concentration, is sufficient for the major pathogens, and is safe for cats. Readers are encouraged to consult guidelines[2] for appropriate disinfectants for a variety of pathogens.

Lighting

The queen is a long day breeder and cycles when the day length increases (February - October in the Northern Hemisphere). During shorter days of the year, cyclicity ceases and queens enter an anestrous stage. Toms have an overall decrease in hormone production and sperm quality during the nonbreeding season; however, it is not substantial enough to affect fertility.[3] When exposed to artificial lighting for 12 - 14 hours per day, cats will continue to maintain cyclicity. Most catteries use a 14:10 hours light:dark schedule. It is noteworthy that in this author's experience, even cats maintained under this lighting system may experience a slight decrease in pregnancy rates during the shorter days of the year. A queen will typically start cyclicity within 1 - 2 months after initiating an artificial lighting period. If cats are exposed to light 24 hours a day, cyclicity will be maintained; however, the number of 'heat cycles' was reduced from 2 per month to only 1.[4] If a group of breeding animals has been maintained under long-term artificial lighting (years) and the overall fertility has declined, allowing the queen to experience a season of anestrus by shortening the lighting period (8 hours of light) for 2 - 3 months may be beneficial before restarting the extended day lighting. Cats housed in a home setting are often exposed to a combination of natural and artificial light. However, animals have the freedom to hide under objects or in dark rooms so the light they are exposed to is variable. Because of this, queens in a house setting will often display seasonality and not exhibit cyclicity during the short daylight period.

Queen

Causes of infertility in the queen are often classified into broad categories and this discussion will focus on those causes that fail to produce a pregnancy despite appropriate breeding management. This discussion will not cover early pregnancy loss that may appear as infertility and must be differentiated from true infertility. Persistent receptivity/estrous behavior, refusal of the male, and ovulation without pregnancy are 3 main categories to explore. A good history can determine which category applies to the patient.

Persistent estrus/receptivity

Persistent estrus and/or receptivity can be identified when a queen either continually displays behavioral signs of estrus, vaginal cytology is > 70% cornified, or she accepts the male continuously. Persistent estrus may appear to occur in queens that naturally display a shorter interestrus period (Siamese) and owners reporting that she is 'in heat all the time'. Daily records of behavior by the owner and a vaginal cytology every 2 - 3 days would determine if the queen is exhibiting normal cyclicity. In a natural breeding situation where the queen is presented to the male, queens that exhibit persistent receptivity are likely failing to ovulate. Failure to ovulate can be suspected based on a history of a female exposed to the male, may or may not have been mated, refuse the male only to begin estrous behavior again 8 - 10 days later. In short, the queen is having normal cyclicity. Ovulation failure may result from lack of adequate stimulation to produce LH surge or a primary ovarian dysfunction (e.g., ovarian follicular cysts). Evaluation of the breeding records, number of witnessed matings, and presence or absence of the 'after reaction' of the queen following coitus will assist in assessing if adequate stimulation has occurred. The 'after reaction' follows intromission and is identified when the female rolls on her back, rubs her face on objects, and licks her perineum. This reaction lasts several minutes while the male usually watches from a distance. A survey of purebred catteries in Sweden determined that only 35% of matings occurred when owners were present.[5] Wireless cameras are a helpful tool to evaluate matings that occurred unobserved. Number and timing of matings that occur when queen is placed with the male will affect ovulation success. Only 1 of 12 cats ovulated with a single mating on day 1 of estrus, whereas 4 of 12 ovulated after a single mating on day 4 of estrus.[6] When 3 matings on a single day were allowed, 10 of 12 cats ovulated on days 1, 2, and 3 of the estrus period.[6] It is generally recommended that 4 or more matings are needed to provide sufficient stimulation and LH release for ovulation to occur. Confirmation of ovulation can be made by evaluating serum progesterone concentrations one week after observed matings. If progesterone concentrations are <less than2 ng/ml, ovulation did not occur and the queen should be back in estrus within a few days. If there is inadequate copulatory stimulation, ovulation may be induced pharmacologically and followed by either natural mating or artificial insemination.

A second cause of persistent estrus is ovarian (follicular) cysts. Ovarian cysts are fluid filled structures producing estrogens that lead to prolonged expression of estrus. Incidence of ovarian cysts increases with age. Presence of cysts is best confirmed by transabdominal ultrasonography.[7] Follicular structures on

the ovary measuring greater than 5 mm in diameter are suspected to be cystic as normal preovulatory follicles measure 2 - 3 mm in diameter. Follicular cysts can be as large as 1 - 2 cm in diameter. Treatment options include attempts to induce luteinization of the cyst(s) by either 500 IU hCG or 25 µg GnRH given intramuscularly. Surgical aspiration or ablation of the cystic structure through laparotomy or laparoscopically have also been reported, with a return to fertility.[8]

Granulosa cell tumors have been reported in the cat and may present as persistent estrus. On ultrasonography, they appear as a mixed echogenic mass. Determination of serum anti-Müllerian hormone concentrations can be helpful in determining the presence of a granulosa cell tumors.

Some overly aggressive males will continuously breed females even after they ovulate. This happens more often when the queen is submissive. Often, the males that overbreed will leave a breeding injury/wound on the back of the queen's neck from the excessive biting. If this is observed, the queen should be removed from the male. Pregnancy can be checked around 30 days later, or serum progesterone can be evaluated one week later to confirm ovulation.

Refusal of a male

When introducing a breeding pair, it is more appropriate to take the queen to the tom, as toms are very territorial. However, if the queen is shy or overly aggressive, she may not allow mating to occur either by fighting or laying on her back when the male approaches. Confirming that the queen is in estrus may make introduction easier. Vaginal cytology will have at least 60% cornified epithelium with small dark nuclei; however, intermediate cells may remain visible and total cornification may not reach 100% as in the dog. The nucleus of the cells become pyknotic, but typically will not disappear completely. If a queen is in estrus but refusing the male, there may be an incompatibility between the pair. Queens in confirmed estrus accepted the male only 39% (15/38) of times.[9] Some queens will be more receptive to the male on day 3 of estrus. Other conditions in the female that may lead to rejection of coitus are vaginal anomalies making breeding excessively painful.

Although queens are induced ovulators, spontaneous ovulation occurs more frequently than originally believed. Incidence of spontaneous ovulations in a group of 15 young queens was 87% over 4.5 months.[10] When a tom was added to the females' room in a separate cage, the incidence of spontaneous ovulations over 10 days increased from 0 - 22% to 33 - 57%. The study concluded that queens housed together can spontaneously ovulate and that frequency increased in the presence of a male. If a female continues to refuse a male, serum progesterone concentrations should be assessed to determine if luteal tissue is present. If progesterone concentrations are > 2 ng/ml, luteal tissue is present.

With pairs that are not compatible, artificial insemination should be performed. Ovulation induction should be followed by semen collection and insemination 24 - 30 hours later. If spontaneous ovulation has occurred, the nonpregnant luteal phase lasts 35-40 days. Queens should be monitored every 1 - 2 weeks utilizing vaginal cytology, behavior, or progesterone assay to determine when the luteal phase has ended. Reintroduction to the male can occur after this period.

Ovulation without pregnancy

Queens that are mated successfully but fail to become pregnant will undergo a 'pseudopregnancy' stage. This is defined as a shortened luteal phase lasting 35 - 40 days instead of the full length of pregnancy. Following mating, ovulation should be confirmed by testing the queen's serum progesterone (> 2 ng/ml) concentrations. Pregnancy diagnosis can be performed via ultrasonography ~ 30 days after mating. Successful mating without pregnancy can be due to either the male or female. A full breeding soundness examination with semen analysis should be performed on the male. Causes in the female are usually due to uterine pathology.

A common primary uterine problem observed in the queen is cystic endometrial hyperplasia (CEH) with or without concurrent pyometra. In the author's research cattery, ~ 75% of queens diagnosed with infertility (failure to produce offspring following appropriately managed breeding[s]) had histological evidence of CEH within their uterus. Clinical signs in this CEH affected group of queens were first noted at 3 - 4 years of age (decreased litter size or failure to produce kittens consistently). Intact female cats over 5 years of age have a greater risk of developing clinical disease associated with CEH/pyometra.[11] An 88% incidence of CEH was observed in cats > 5 years old compared to 30% in cats aged 2 - 4, with a much greater incidence of the disease in colony raised cats compared to feral cats.[12] Diagnosis is suspected based on history of reduced fertility. A thickened uterine wall with prominent endometrial folds and small cystic areas within the uterus may be observed on ultrasound. A uterine biopsy provides definitive diagnosis and may be required for less severe cases. Currently, uterine biopsy is best obtained surgically. If CEH is severe, prognosis for fertility is guarded and ovariohysterectomy is recommended. Pyometra often occurs secondary to CEH and may result in ovariohysterectomy (preferred treatment for older queens not needed for future breeding). However, unlike observed in the bitch, queens are often not systemically ill and the only clinical sign may be a purulent vaginal discharge. Treatment with a fluroquinolone, native prostaglandin, and cabergoline can provide appropriate successful medical treatment. Medical management of pyometra in the queen should be performed on a case-by-case basis. Underlying CEH cannot be corrected.

Subclinical endometritis may also cause infertility in the cat. It has become a leading cause of infertility in the bitch. Among biopsy samples from 399 intact bitches, the most common lesion observed was endometritis (42.6%).[13] Although there is less information describing this lesion in the queen, it is likely that this pathology is also a substantial cause of infertility in this species.

Miscellaneous causes

There are countless other potential causes of infertility or early pregnancy loss in the queen. Infectious (bacterial and viral) should be ruled out with serology and culture. Vaginal culture may be obtained but should be interpreted with caution due to high likelihood of contamination when swabbing the

caudal vaginal canal. A cranial vaginal sample would be ideal; however, when in estrus, the queen's cranial vagina measures only 1 - 2 mm in diameter when compared to 4 mm of the caudal vagina, making sampling difficult.[14] If a pure culture is obtained, treatment would be indicated based on the susceptibility pattern. Pure or heavy growth of *ß-hemolytic streptococci* or *Escherichia coli* has been associated with endometritis and pyometra. *Mycoplasma sp*., *Ureaplasma sp.*, *Coxiella burnetti*, and *Chlamydia sp.* have all been implicated in infertility. A PCR test is the most sensitive assay for these bacteria and diagnosis should be based on results and clinical signs. Treatment with antibiotics should be reserved for animals exhibiting clinical signs and based on susceptibility of the positive culture.

Tom

When evaluating infertility in a pair, the tom is the easier to evaluate. A complete breeding soundness examination should be performed starting with history, general physical examination, and external reproductive examination. Puberty occurs between 7 - 12 months. Prior to puberty, adhesion of the balanopreputial fold prevents full exposure of the penis. Breakdown is androgen dependent and therefore makes this an initial reference point for pre versus post pubertal animals.[15] Androgen dependent penile spines are present on the proximal ⅔ of penis indicating the presence of circulating testosterone. Testes should be located within the scrotum and be freely movable. Scrotal skin should be free from dermatitis or wounds. Both testes should palpate slightly firm and of similar size. Ultrasonography of the testes should be performed after palpation. Testes should be round to slightly oval. Literature relating size of the testes to fertility is lacking in the tom but can be inferred based on other species. Average daily sperm output for a standard tom has been estimated at 32 x 10^6.[16] Via ultrasonography, length, width, and height of each testis should be measured and the testicular volume (TV) calculated using the formula for an ellipse simplified to TV = 0.2533 x Length x Width x Height). The process for placement of the ultrasound probe for measuring has been described.[17] These measurements are most helpful when evaluating testicular size in a single tom over time rather than a comparison among males.

Semen collection in the tom is more difficult than other domestic species. Collection using a home-made artificial vagina was first reported in the 1970s.[18] In a clinic setting, collection using an artificial vagina is not practical unless the tom has been previously trained. The most effective method of semen collection is electroejaculation. The process this author uses has been described.[19] Although electroejaculation is the most consistent in obtaining sperm from the tom, it requires specialized equipment that may not be available in all clinics. The most practical method of obtaining a semen sample in the clinic setting is urethral catheterization after pharmacological induction. This technique was described using a high dose of medetomidine (120 µg/kg).[20] Since medetomidine is no longer available in the US, dexmedetomidine can be used at a comparable dose (60 µg/kg). Lower doses of both medications were studied (50 µg/kg medetomidine and 25 µg/kg dexmedetomidine) but the sedation level and ejaculate collection were inadequate.[21] Once full sedation is achieved (cat in lateral and unresponsive), an open ended tomcat catheter should be inserted into the urethra 8 - 9 cm. Measuring and marking the catheter prior to insertion will assist with proper placement. Care must be taken not to enter the bladder. A single catheterization inserted and immediately removed following full sedation was preferrable to multiple catheterization attempts and provided an adequate sperm sample without damaging the urethra.[22] The sample can be flushed from the catheter using an appropriate extender. This author prefers making extender using Ham's F-10 with 25 mM Hepes, 1mM pyruvate and glutamine, and 5% fetal bovine serum. An alternative that is commercially available is TEST yolk buffer (refrigeration media, Irving Scientific). However, analysis of the motion characteristics may be difficult due to the interface egg yolk droplets if the extender is not filtered prior to use. Once the sample is obtained, a complete sperm analysis should be performed including motility, morphology, and cytology to evaluate for inflammatory cells.

Causes of infertility in the male can be classified into unable/refusal to mate and mating but not achieving pregnancies. If the male displays reduced libido, it could be due to stress, an overly aggressive female, or systemic disease. Apart from history and physical examination, routine blood work should be performed. Female should be removed from the male to allow the male to rest. A second female or the same female after confirming that she is in estrus can be returned several days later. If male is refusing to breed a female, physical limitations should be addressed (e.g. sore back or mouth). Primary penile problems (e.g. persistent frenulum, hair ring, priapism, or paraphimosis) should also be evaluated. Observation of the interaction between the male and female is ideal to assess behavioral problems with the male alone, or the pair.

Failure to produce litters

For toms that are breeding naturally, inducing ovulation, but not achieving pregnancies, a semen analysis is vital. Teratospermia, defined as > 40% abnormal sperm, is observed in small populations of cats where inbreeding or excessive line breeding has occurred.[23] A single generation of inbreeding (offspring bred to parent) produced male offspring with < 15% morphologically normal sperm compared to 55% morphologically normal sperm in control animals, indicating that loss of genetic diversity leads to increased teratospermia in as short as 1 generation.[23] Unlike in other species, many teratospermic ejaculates in the tom demonstrate adequate motility (> 70%), in spite of low numbers of morphologically normal sperm. Because the tom breeds multiple times a day, even toms that are classified as teratospermic may have normal fertility.

Azoospermia is the complete absence of sperm in the ejaculate. To differentiate this from ejaculation failure, seminal plasma alkaline phosphatase concentrations can be determined. A higher alkaline phosphatase (typically > 5,000 IU/l) concentration confirms that the sample has originated from the epididymis and a complete ejaculate was obtained. If azoospermia is confirmed, prognosis for return to fertility is poor unless a treatable underlaying disease is diagnosed. The tom should have a second semen evaluation 2 - 3 months later to detect improvement.

Culture of the ejaculate may be indicated if inflammatory cells are identified in the ejaculate. A pure culture should be a cause for concern and should be treated based on susceptibility.

Conclusion

Infertility in the queen and tom can be multifactorial. History and examination can help to prepare a differential list that leads to diagnosis of the specific problem. Treatment varies and should be directed at the specific cause, if identified.

Conflict of interest

None to declare.

References

1. Johnson AK: Normal feline reproduction: The queen. J Feline Med Surg 2022;24:204-211.
2. Stull JW, Bjorvik E, Bub J, et al: 2018 AAHA Infection Control, Prevention, and Biosecurity Guidelines. J Am Anim Hosp Assoc 2018;54:297-326.
3. Tsutsui T, Onodera F, Oba H, et al: Plasma hormone levels and semen quality in male cats during non-breeding and breeding seasons. Reprod Domest Anim 2009;44(Suppl 2):291-293.
4. Leyva H, Madley T, Stabenfeldt GH: Effect of light manipulation on ovarian activity and melatonin and prolactin secretion in the domestic cat. J Reprod Fertil Suppl 1989;39:125-133.
5. Strom Holst B, Frossling J: The Swedish breeding cat: population description, infectious diseases and reproductive performance evaluated by a questionnaire. J Feline Med Surg 2009;11:793-802.
6. Wildt DE, Seager SW, Chakraborty PK: Effect of copulatory stimuli on incidence of ovulation and on serum luteinizing hormone in the cat. Endocrinology 1980;107:1212-1217.
7. Davidson AP, Baker TW: Reproductive ultrasound of the bitch and queen. Top Companion Anim Med 2009;24:55-63.
8. Johnston SD RKM, Olson PS: Canine and Feline Theriogenology. Philadelphia, PA; Saunders: 2001.
9. Root MV, Johnston SD, Olson PN: Estrous length, pregnancy rate, gestation and parturition lengths, litter size, and juvenile mortality in the domestic cat. J Am Anim Hosp Assoc 1995;31:429-433.
10. Gudermuth DF, Newton L, Daels P, et al: Incidence of spontaneous ovulation in young, group-housed cats based on serum and faecal concentrations of progesterone. J Reprod Fertil 1997;51(Suppl):177-184.
11. Potter K, Hancock DH, Gallina AM: Clinical and pathologic features of endometrial hyperplasia, pyometra, and endometritis in cats: 79 cases (1980-1985). J Am Vet Med Assoc 1991;198:1427-1431.
12. Perez JF, Conley AJ, Dieter JA, et al: Studies on the origin of ovarian interstitial tissue and the incidence of endometrial hyperplasia in domestic and feral cats. Gen Comp Endocrinol 1999;116:10-20.
13. Gifford AT, Scarlett JM, Schlafer DH: Histopathologic findings in uterine biopsy samples from subfertile bitches: 399 cases (1990-2005). J Am Vet Med Assoc 2014;244:180-186.
14. Zambelli D, Cunto M: Vaginal and cervical modifications during the estrus cycle in the domestic cat. Theriogenology 2005;64:679-684.
15. Margaret V. Root SDJ, Gary R. Johnston, Patricia N. Olson: The effect of prepubertal and postpubertal gonadectomy on penile extrusion and urethral diameter in the domestic cat. Vet Radiol Ultrasound 1996;37:363-366.
16. Franca LR, Godinho CL: Testis morphometry, seminiferous epithelium cycle length, and daily sperm production in domestic cats (Felis catus). Biol Reprod 2003;68:1554-1561.
17. Johnson AK: Normal feline reproduction: The tom. J Feline Med Surg 2022;24:212-220.
18. Sojka NJ, Jennings LL, Hamner CE: Artificial insemination in the cat (Felis catus L.). Lab Anim Care 1970;20:198-204.
19. Johnson AK: Evaluation in the tom: collection procedures, evaluation of sperm, and subsequent use. Clinical Theriogenology 2014;3:219-223.
20. Zambelli D, Prati F, Cunto M, et al: Quality and in vitro fertilizing ability of cryopreserved cat spermatozoa obtained by urethral catheterization after medetomidine administration. Theriogenology 2008;69:485-490.
21. Cunto M AGE, Ballotta G, and Zambelli D: Effect of medetomidine and dexmedetomidine administration at different dosages on cat semen quality using Urethral Catheterization after Pharmacological Induction (Ur.Ca.P.I.). Reproduction in Domestic Animals 2019;54:96-97.
22. Cunto M, Kuster DG, Bini C, et al: Influence of Different Protocols of Urethral Catheterization after Pharmacological Induction (Ur. Ca.P.I.) on Semen Quality in the Domestic Cat. Reprod Domest Anim 2015;50:999-1002.
23. Pukazhenthi BS, Neubauer K, Jewgenow K, et al: The impact and potential etiology of teratospermia in the domestic cat and its wild relatives. Theriogenology 2006;66:112-121.