



Current concepts on infertility in the bitch



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KEY POINTS

- ◆ Infertility in the bitch is most commonly due to inappropriate breeding management rather than an inability to conceive or carry a litter to term
- ◆ Considerable variation exists within the normal canine reproductive cycle; breeders commonly interpret such variation as an indication that an abnormality exists. The clinician must differentiate bitches having normal estrus cycles with unexpected patterns from those with true abnormalities
- ◆ Evaluation of the estrus cycle for actual abnormalities is an important component in assessing the suspected infertile bitch; variations from normal estrus cycle events can sometimes be traced to specific ovarian disorders
- ◆ A complete evaluation of a bitch's reproductive potential must often be delayed until an estrus cycle occurs

Introduction

Infertility in the bitch refers to the inability to conceive and produce viable offspring. Most of the bitches presented to reproductive practice for infertility are normal, their failure to conceive is instead due to breeding management or stud dog

problems. Considerable variation exists within the normal canine reproductive cycle and breeders commonly interpret such variation as an indication that an abnormality exists. The clinician must differentiate bitches having normal estrus cycles with unexpected patterns from those with true abnormalities. Detection of individual variation within the normal range of events in a fertile bitch can be crucial to providing effective counseling concerning breeding management. Additionally, evaluation of the estrus cycle for actual abnormalities is an important component in assessing the apparently infertile bitch. Variations from normal estrus cycle events in the bitch can sometimes then be traced to specific ovarian disorders.

History and physical examination, data base

The complete history of the bitch should be obtained and it is important to be thorough, including not only the reproductive and breeding management history, but also the general health history. A thorough physical examination should be completed before beginning a focused evaluation of the reproductive system. A minimum database consisting of a complete blood count, serum biochemistry profile, urinalysis (with culture if indicated), and *Brucella canis* screening (in those countries where this is appropriate) should be evaluated for evidence of systemic disease. Vaccination

and deworming history and heartworm status should also be assessed (1-3).

Reproductive physiology

A solid understanding of the bitch reproductive cycle, described below, is essential when evaluating a breeding bitch for infertility.

Puberty

Normal puberty can occur at 6-24 months, and larger dogs tend to reach puberty at an older age than smaller dogs. The first estrus can be irregular and split heats are common, reflecting a period of folliculogenesis without ovulation occurring. Between 2 weeks and 2 months later, a normal, ovulatory cycle usually occurs. Delayed puberty is rare in the bitch and that which is a consequence of a nutritional etiology has a poor prognosis for future fertility. The first estrus cycle can sometimes be hastened by housing the bitch with a kennelmate that is in proestrus, due to the pheromone effect; medical induction can be attempted in an otherwise normal bitch (4, 5).

The interestrus interval

Interestrus consists of diestrus, typically lasting 45-60 days, and anestrus, which is very variable, although usually between a 90 and 150 days duration. Thus, the average duration of interestrus is 7 months. German Shepherd bitches average about 6.5 months interestrus, Dachshunds average about 8.3 months interestrus, and in general larger dogs tend to have shorter interestrus intervals than small dogs. Variation in the interestrus interval is not abnormal. Interestrus tends to become longer as bitches age beyond 8 years. Seasonality may exist in the bitch, with cycles more common in the summer and winter (4, 5).

The estrus cycle

The stages of the canine estrus cycle are anestrus, proestrus, estrus, and diestrus. Anestrus is a time of mandatory endometrial repair after progesterone has exerted a proliferative effect during diestrus for the preceding 45-60 days. Fertility is low if at least a 90 day anestrus (or a 150 interestrus interval) is not attained, because the uterus has not repaired enough from diestrus to subsequently establish and maintain pregnancy.

During anestrus the male shows no sexual interest in the female. The female shows no sexual interest in the male. The vulva is not swollen or edematous. Vaginal cytology is hypocellular with noncornified parabasals (See Cut-out

and Keep guide on page 39). The vaginal wall is very thin and appears pale on vaginoscopic examination. Progesterone is at baseline concentration (<1 ng/mL). Note that even spayed bitches have basal levels of progesterone, probably of adrenal origin. Prolactin secretion by the pituitary may promote anestrus, because prolactin inhibitors can be used to terminate anestrus. The termination of anestrus is associated with an increased pulse frequency of LH and increased FSH late in anestrus.

Proestrus averages 9 days in duration, but may last 3-17 days. Males are interested in the female but females show no interest in the males. The vulva is swollen because of estrogen secretion by the growing follicles. There is serosanguinous discharge from the vulva that results from diapedesis of erythrocytes through uterine vessels. Vaginoscopically, the vaginal mucosa appears smooth because estrogen causes edema. LH pulses have an increased frequency and FSH is suppressed. Estrogen originates from the growing follicles and peaks at the end of proestrus. It is actually the decline in estrogen at the end of proestrus that causes the bitch to show clinical signs of estrus (receptivity). Interestingly, testosterone is relatively high at the end of proestrus, perhaps resulting from a 'backup' in estrogen synthesis. This may result in some masculine behavior by the bitch, such as mounting other dogs. The proestrus vaginal cytology demonstrates an increase in cornification of approximately 10%/day until about 100% of the cells are cornified (See Cut-out and Keep guide on page 39). Erythrocytes and a bloody vulval discharge are variably present and even if there is a bloody discharge apparent grossly, erythrocytes may not appear on vaginal cytology. Visualized vaginoscopically, the vaginal mucosa is glistening with rounded edges to the mucosa because of cellular edema.

Estrus averages 9 days in duration, but can be as short as 3 days or as long as 21 days. The male and female are both interested in each other. The bitch will 'flag' her tail, as a sign of receptivity. The estrus behavior results from the estrogen that peaked during proestrus abruptly declining while progesterone is rising. The estrual vaginal cytology is very cellular and greater than 90% of the cells are cornified. Most of the cells are anuclear. Neutrophils are absent because the hyperplastic vaginal wall is too thick for them to cross the mucosa. Erythrocytes are often absent. The background of the smear becomes very clean. The cells may slough off as sheets as the end of estrus approaches. Vaginal vaginoscopy reveals the vaginal epithelium with a

wrinkled appearance (crenelation) owing to the acute fall in estrogen concentrations which results in dehydration of the mucosa.

The LH peaks about 24-48 hours into estrus and is triggered by the estrogen peak during proestrus. The LH peak causes ovulation of the follicles. The LH peak has a very short duration and it must be assayed every day in order to detect it. Ovulation occurs 24-48 hours after LH peak (day 3-4 of estrus) and takes about 24 hours for completion. The fertile period of breeding is generally recommended as the 3rd through the 5th-6th day after the LH surge, covered by breeding every other day of estrus.

Progesterone starts to rise during estrus and the initial rise usually coincides with the LH peak. The preovulatory rise in progesterone is caused by estrual luteinization of follicles and a 'backup' in progesterone from the estrogen synthesis. The progesterone rise that coincides with the LH peak can be measured every other day, and can be used to predict the fertile period. Since progesterone starts to rise coincidentally with the LH peak, when estrus ends, the progesterone is already greatly elevated over baseline. Diestrus is then the time of progesterone dominance.

Diestrus in the non-pregnant bitch could be called covert pseudopregnancy, since progesterone remains elevated, but there are no signs of pregnancy. During diestrus the bitch refuses male's advances. Bitches may remain receptive after the fertile period. At the beginning of diestrus there is an abrupt change from the 100% to less than 50% cornification, marking the first day of diestrus. Neutrophils return to clean up all the sloughed cells and debris. Intermediate cells return as well as 'metestrus' cells and foam cells. Progesterone is secreted by the *corpora lutea*, the only source of progesterone in the bitch. Prolactin in diestrus is higher in pregnant bitches than in non-pregnant bitches. It rises with the decline in progesterone in both pregnant and non-pregnant bitches. Prolactin causes mammary development. The cessation of diestrus is not known to be associated with PGF secretion from the uterus in non-pregnant bitches (4, 5).

Differential diagnosis for infertility: management problems and a protocol for clinical ovulation timing

Bitches presented for failure to permit breeding or failing to conceive after a forced breeding, or artificial insemination, during the perceived fertile period need to be evaluated first for kennel management errors.

The timing of receptive and fertile periods during estrus varies significantly among normal bitches and even in individual bitches during different estrus cycles. These periods may not correlate with the handler's choice of predetermined breeding dates, typically between days 10-14 after the onset of vaginal bleeding. Ovulation timing protocols utilizing serial vaginal cytology, repeated vaginoscopy and serum progesterone and LH concentrations are useful in identifying the actual fertile period when breeding should occur, allowing evaluation of breeding management decisions (1, 6).

Breeder clients should be advised to notify the clinic when they first notice that the bitch under evaluation is in season, based on vaginal discharge or vulval swelling/attraction to males. Even the most astute owner can fail to notice the true onset of proestrus for a few days. Early proestrus should be documented by vaginal cytology (<50% cornification/superficial cells). A baseline progesterone level might be informative if the true onset of the cycle is unknown (usually 0-1 ng/mL in proestrus). Vaginal cytology should be performed every 2-4 days until a significant progression in cornification is seen, usually >70% superficial cells. At that point, serial hormonal assaying should begin. For routine breedings, progesterone testing may be done every other day, until a rise in progesterone >2 ng/mL is identified. This day of the initial rise in progesterone is identified as day "zero". Breedings are advised on days 2, 4 and 6 (1, 5, 7).

When increased accuracy of ovulation timing is necessary (e.g. frozen or chilled semen breedings, bitch infertility cases, breedings with subfertile stud dogs) daily LH testing is recommended if available. Once the LH surge is identified, breeding days may be planned based on the basis that this is called day "zero". As with progesterone testing, vaginal cytology dictates when to begin LH testing (>70% superficial cells). Vaginal cytology may be continued until the diestral shift is identified, which gives a retrospective evaluation of the breeding just completed (LH peak likely 7-9 days previously). In addition, at least one progesterone assay should be performed after the LH surge or when indicative initial rise in progesterone is identified. The purpose is to document that levels continue to rise above 5 ng/mL, confirming ovulation and luteinization. Extended chilled breedings should occur on days 4 and 6, or 3 and 5 after day "zero". Which two days are chosen can depend upon overnight shipping possibilities and the involved clients' schedules. Frozen semen breedings should occur day 5 or 6 after day "zero" (8).

If client economics dictate minimal testing, serum can be batched on a daily basis and quantitative progesterone tests performed as advised above. When the initial rise in progesterone is identified, the batched serum can be specifically evaluated for the day of the LH surge, confirming identification of day “zero”.

Vaginoscopy may be performed throughout the cycle as an adjunct to vaginal cytology and hormonal assays, especially when evaluating an unusual cycle. Behavior and other observations should also be made at each examination, but less weight should be put on these parameters. The clinician should keep in mind that the most accurate ovulating timing occurs when information from several tests is pooled (vaginal cytologies, vaginoscopy, and progesterone or LH tests) (9).



Figure 1.
Ultrasonographic image of a canine ovary with multiple follicles.
(Courtesy A. Fontbonne / National Veterinary School of Alfort, France).



Figure 2.
Ultrasonographic image of a canine ovary immediately post ovulation.
(Courtesy A. Fontbonne / National Veterinary School of Alfort, France).

Ultrasonography may be used to help identify ovulation in the bitch. Early attempts were discouraging; the small size of the ovaries and their similarity to close structures made them difficult to visualize. However, recent reports have identified ovulation as occurring when a detectable decrease in the number of hypoechoic follicles is seen during serial imaging (3 times daily) (**Figures 1 and 2**). The data has shown a close correlation to the ovulation time established by LH and progesterone levels (See article from A. Fontbonne and E. Malandain page 22) (8, 9).

Behavioral or physical problems can interfere with a bitch’s acceptance of a male for breeding. Dominant bitches exposed to an inexperienced male may not allow breeding even during the appropriate time. Vulval or vaginal abnormalities such as strictures and septate bands, and vaginal hyperplasia may make natural breeding painful and result in a bitch refusing to permit copulation even when in estrus (**Figures 3 and 4**). The pre-breeding veterinary examination permits early detection of such anatomic problems, enabling their correction or adjustment in breeding plans (artificial insemination *versus* natural) before the onset of proestrus (1-3).

Male problems

Fertility of the male must be confirmed before initiating an infertility work-up on the bitch failing to become pregnant. Although physical findings and semen evaluation including sperm count, morphology and motility are helpful, there is no method for evaluating sperm function other than a history of conception with other bitches close to the time a stud dog is bred to the bitch with infertility concerns (10).

True infertility

Abnormal estrus cycles

Abnormal estrus cycles can be categorized and simplified into several patterns reflecting either a prolongation or



Figure 3.
Vestibulovaginal septate stricture.



Figure 4.
Vaginal hyperplasia.

abbreviation of a phase of the cycle, or an alteration in the normal sequence of events. An owner's interpretation of a bitch's behavior and physical characteristics may not equate with the actual physiologic events, necessitating prospective documentation of the cycle through vaginal cytology, vaginoscopy, behavioral analysis and serum progesterone and LH levels when the bitch is in season (11).

Prolonged proestrus/estrus

Prolonged proestrus or estrus occurs when a bitch displays vaginal bleeding for more than 21-28 consecutive days, accompanied by attractiveness to males. Greater than 80-90% superficial cells are found on vaginal cytology. Such bitches may or may not be receptive to breeding. Prolonged proestrus and/or estrus most likely results from persistent secretion of estrogens, with or without small elevations in progesterone secretion. If secreted, progesterone enhances the presence of sexual receptivity.

Endogenous sources of prolonged estrogen exposure in the bitch, with or without progesterone, include ovarian follicular cysts and secretory ovarian neoplasias, and theoretically, adrenal gland origin. Secretory, anovulatory follicular ovarian cysts tend to be solitary, lined with granulosa cells, and exceed normal preovulatory follicles in size, ranging from 1 to 5 cm in diameter (**Figure 5**). Bilateral follicular cysts can indicate a problem with the hypothalamic pituitary ovarian axis. Follicular cysts tend to occur in bitches <3 years of age. Ovarian neoplasias capable of producing estrogen occur and include tumors of epithelial origin (cystadenomas and adenocarcinomas) as well as tumors of gonadal-stromal origin (granulosa-theca cell tumors) (**Figure 6**). Ovarian neoplasia tends to occur in bitches >5 years of age. Ovarian tumors can occur unilaterally or, less commonly, bilaterally. Functional ovarian neoplasia and cystic ovarian pathology can occur simultaneously. Cysts found in the contralateral ovary and endometrial hyperplasia accompanying a functional tumor occur most frequently with gonadal-stromal origin tumors. Adrenal disorders causing hyperestrogenism are rare (11).

There are few differential diagnoses for prolonged vaginal bleeding:

- Vaginal bleeding secondary to infection, inflammation or neoplasia of the genitourinary tract
- Vaginal foreign bodies
- Coagulopathy

These differentials should be differentiated from

prolonged proestrus or estrus due to ovarian disease. Excessive exogenous (iatrogenic) administration of estrogen may be encountered when a bitch is treated for urethral sphincter incompetence with diethylstilbestrol (DES), or from attempts to prevent unwanted pregnancy using DES or estradiol cypionate.

After confirmation of naturally occurring hyperestrogenism is obtained through vaginal cytologies (they can be confirmed with serum estrogen level measurement), abdominal ultrasonography is recommended in the attempt to identify an ovarian follicular cyst or functional neoplasia. Normal preovulatory follicles usually measure 4 to 9 mm in diameter, smaller than most follicular cysts and most functional neoplasias. Analysis of the estrogen and progesterone levels in fluid from abnormal cystic ovarian structures can confirm the diagnosis. These analyses are obtained via ultrasound guidance and histologic analysis of tissues obtained surgically. Estradiol levels from cysts are usually much higher than serum levels (9, 11).

Because follicular cysts may spontaneously undergo atresia or luteinization, not all bitches experiencing prolonged proestrus or estrus require treatment. Progression of the



Figure 5.
Ultrasonographic image of an ovarian follicular cyst. (Courtesy T. Baker).



Figure 6.
Ultrasonographic image of a functional ovarian tumor. (Courtesy T. Baker).

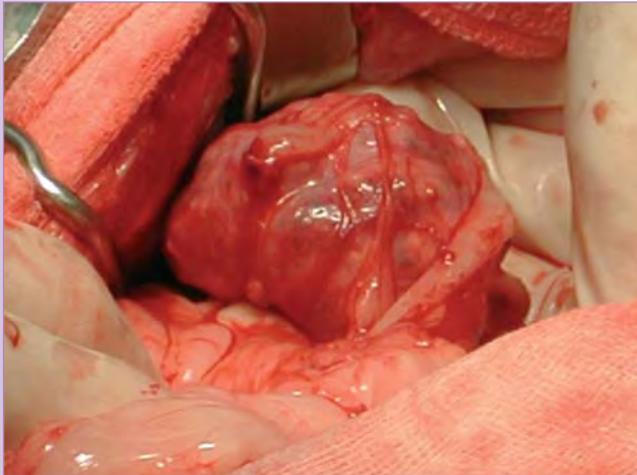


Figure 7.
Multiple luteal cysts in the ovary of a bitch.

follicular cyst to an atretic follicle or a *corpora lutea* can be monitored ultrasonographically, via vaginal cytologies, by serum estrogen and progesterone levels.

Therapy aimed at terminating prolonged proestrus or estrus becomes necessary if spontaneous regression fails to occur, vaginal bleeding is a continuing nuisance, estrus behavior and the attraction of males is unacceptable, or other complications develop (blood loss anemia, marrow dyscrasias, vaginal hyperplasia). Medical and surgical options exist for treatment of persistent pathologic follicular cysts. Medical therapies should not place the reproductive health of the bitch at risk:

- Progesterone treatment of bitches with functional follicular cysts puts the bitch at increased risk for the development of cystic endometrial hyperplasia/pyometra, and is not advised.
- The use of GnRH (50-100 µg/bitch IM every 24-48h for up to 3 doses) or human placental gonadotropin (hCG; 22 IU/kg, IM, every 24-48h) has been advocated as affective in inducing cyst regression or luteinization, although reported success rates for either vary. GnRH does not appear to be antigenic in the bitch, and may be the preferred treatment.

Successful induction of cyst regression or luteinization is



Figure 8.
Ultrasonographic image of cystic endometrial wall changes. (Courtesy T. Baker)

reflected by a reduction in vaginal discharge and vulval enlargement, change in vaginal cytology reflecting reduced estrogen effect, diminished attractiveness to males, and normalization of behavior. Serum estrogen concentrations fall, and increased progesterone concentrations can occur if luteinization results, but this is variable. Ultrasonographic monitoring of ovarian morphology shows regression of hypoechoic structures. It has been suggested, but not proven, that failure of medical therapies to resolve prolonged proestrus or estrus indicates that ovarian neoplasia is more likely than a follicular cyst. However, medical treatment of prolonged proestrus or estrus is usually unrewarding and surgical removal of the cyst the most expedient means of managing the problem. Removal of the cyst alone is optimal, but resection of the associated ovary is usually necessary. Histologic evaluation of the removed tissue confirms the diagnosis and, more importantly, permits evaluation for evidence of neoplasia that might warrant additional therapy and a different prognosis (11).

Prolonged interestrus intervals

Bitches exhibiting prolonged interestrus intervals may have prolongation of either anestrus or diestrus. Prolonged anestrus occurs when no ovarian activity occurs for longer than 16 to 20 months in a bitch having previously experienced estrus cycles (secondary anestrus). An actual failure to continue to cycle must be differentiated from silent heats (normal cycles not

Table 1.
Drugs utilized for reproductive disorders

GENERIC	DOSAGE	ROUTE / FREQUENCY	DESCRIPTION
GnRH	50-100 µg IM	q 24-48h x 3	Hypothalamic releasing hormone
hCG	22 IU/kg IM	q 24-48h	Placental gonadotropin
PGF2α	0.10-0.20 mg/kg SC	q 8-12h	Natural prostaglandin
Bromocriptine	0.01-0.10 mg/kg	divided bid	Antiprolactin
Cabergoline	5.0 µg/kg po	q 24h or divided bid prn	Antiprolactin

detected by the owner). Underlying disease and iatrogenic causes for failure to cycle should be ruled out by a careful history, physical examination and database. The mechanism by which anestrus is normally terminated in the bitch is not well understood. Dopamine inhibits prolactin secretion and prolactin levels decrease from late diestrus to late anestrus. Both FSH and LH have been reported as the hormone initiating proestrus folliculogenesis. Dopamine agonists (cabergoline, bromocriptine) can be used to shorten anestrus in both the normal bitch and in bitches with secondary anestrus of unknown etiology (**Table 1**). The mechanism by which dopamine agonists induce proestrus may be a direct reduction in prolactin levels or a direct dopaminergic action on either the gonadotrophic axis or on ovarian gonadotropin receptors (4, 10, 11).

A bitch presented for evaluation of prolonged intervals between heat cycles may be under the influence of elevated progesterone concentrations (>2 to 5 ng/mL). When progesterone levels remain elevated for longer than 9 to 10 weeks, prolonged diestrus is probable. The clinical behavior of the bitch cannot be differentiated from one experiencing prolonged anestrus. The value of vaginal cytologies, serial serum progesterone levels and the ultrasonographic appearance of the ovaries and uterus become apparent in establishing a diagnosis.

Prolonged diestrus can occur secondary to the presence of a luteinized (progesterone secreting) ovarian cyst. The progesterone presents negative feedback to the pituitary/hypothalamic axis, preventing the stimulation of normal ovarian activity. Luteinized cysts can be single or multiple, involving one or both ovaries (**Figure 7**). Abdominal ultrasonography can identify hypoechoic structure(s) within the affected ovary (ies) and uterine wall changes resulting from prolonged progesterone exposure (**Figure 8**). Abdominal radiography rarely provides diagnostic information because the cysts are relatively small. Serum progesterone levels >2-5 ng/mL confirm the diagnosis. Treatment with prostaglandin F2alpha (PGF2α) usually causes only a transient decline in serum progesterone levels, indicating partial luteolysis. Surgical removal of the cyst(s) with histologic analysis is the recommended treatment. Separation of the cyst from the affected ovary is optimal but is technically difficult, usually necessitating ovariectomy. Acquiring a uterine biopsy to evaluate the presence and extent of accompanying cystic endometrial hyperplasia is advisable, as it can provide valuable information to the owner concerning future fertility of the bitch, however, normal diestrual endometrial changes must be kept in

mind, and evaluation in anestrus is likely to be more informative, but requires a second procedure. Cystic endometrial hyperplasia, if present, may resolve partially after elimination of the cyst (11).

Nonfunctional ovarian cysts may cause failure to cycle due to their mass effect. *Rete ovarii* cysts and subsurface epithelial structure cysts are examples of such nonfunctional ovarian cysts. Increases in plasma estrogen or progesterone levels will not be identified, although these cysts have the potential to produce a wide variety of other steroidal compounds without systemic effect. This diagnosis, initially suspected using abdominal ultrasonography, is confirmed by histologic evaluation of surgically removed tissues (11).

Premature ovarian failure can result in permanent anestrus. Although the functional longevity of the ovaries of bitches is not known, on average the decline in function would not be expected before 7-10 years of age. Prolonged anestrus due to premature ovarian failure could be supported by documenting markedly elevated FSH and LH concentrations as would be seen following ovariectomy. Such increases indicate a lack of negative feedback to the pituitary and hypothalamus, without any other identifiable cause for anestrus. Immune mediated oophoritis, diagnosed by ovarian histopathology, could result in prolonged anestrus. A mononuclear infiltrate predominated by lymphocytes, plasma cells and macrophages has been reported to occur in both ovaries in a bitch experiencing estrus cycle abnormalities. This is an extremely rare disorder (11). Failure to cycle can occur with disorders of sexual differentiation (**Figure 9**) (10).

Hypothyroidism is a potential cause for failure to cycle, but the diagnosis should be well supported by other clinical signs (lethargy, weight gain, bilaterally symmetric alopecia) and clinical pathologic data



Figure 9.
Os clitoridis in a bitch exhibiting failure to cycle.
(Courtesy Dr. A Hughes).

(hypercholesterolemia, nonregenerative anemia), as well as confirmation of subnormal serum thyroid (total T4 and free T4 by equilibrium dialysis) levels, ideally supported by elevated endogenous canine TSH levels. Hypothyroid bitches placed on adequate replacement therapy should begin to cycle within six months of becoming euthyroid. The breeding soundness of such bitches should be addressed with clients. Glucocorticoids can feedback on pituitary gonadotropins FSH and LH, causing a failure to cycle. Therefore, administration of any steroid medication must be discontinued in a bitch with prolonged anestrus (11, 12).

Shortened interestrus intervals

Bitches with short interestrus intervals (less than 4.5 months) can fail to conceive due to incomplete uterine involution and repair, precluding implantation and pregnancy maintenance. Classically, bitches experiencing shortened interestrus intervals are normal in other respects. Ovulation and luteinization occur, the secondary oocyte is fertilized (difficult to document clinically) but fails to implant successfully. Documentation of this disorder requires evaluation of serial vaginal cytology during estrus and diestrus, and serum progesterone levels during the luteal phase of at least 2 consecutive cycles. Currently, there is no reliable, commercially available, consistent pre-implantation method of confirming fertilization in the dog. The occurrence of folliculogenesis without ovulation (split heat) and hypoluteiodism (premature luteal failure) should be ruled out.

Shortened interestrus intervals occur because anestrus is abbreviated. A defect in the hypothalamic-pituitary-ovarian axis may exist, causing interference with the normal maintenance of anestrus, or an imbalance of dopamine *versus* prolactin levels have been theorized as contributing to this syndrome. Anestrus can be abbreviated clinically in the normal bitch by the administration of prolactin inhibitors such as cabergoline and bromocriptine. Intervention should not take place unless the bitch is older than 3 years, because these abnormalities may naturally resolve with maturity. One suggested therapy consists of prolonging anestrus through the use of megestrol acetate during the first three days of the impending estrus, but the use of progestational compounds in reproductively valuable bitches is risky due to the potential for inducing uterine pathology (10, 11, 13, 14).

Other causes of infertility

Uterine disorders

Uterine pathology, such as cystic endometrial hyperplasia (CEH), must be considered as a cause of infertility should all other possibilities be excluded. Interestingly, uterine disease is less of a problem in breeding establishments where bitches are bred and conceive on a regular basis, as pregnancy may have a protective effect on the endometrium (10, 13).

Cystic endometrial hyperplasia is a hormonally dependent, predictable condition in the bitch that results from repeated cycles of progesterone stimulation inducing endometrial glandular proliferation and secretion. Glandular changes may be focal or diffuse and may interfere with implantation and placentation. Pyometra can eventually result. Definitive diagnosis of CEH requires biopsy at an affected site. Ultrasonography of the uterus can be very helpful in evaluating the uterine wall structures over time. Hydrometra or mucometra can be precursors to CEH and subsequent pyometra. All three disorders carry a poor prognosis for fertility (13).

Open cervix pyometra in a valuable breeding bitch in her prime can be treated with specific antibiotics (as indicated by culture and sensitivity) and PGF2 α induction of luteolysis and uterine evacuation (0.1 mg/kg sc bid for 2 days, then 0.2 mg/kg sc bid to effect). Breeding on the next cycle is advised (15).

Infectious disease

Infectious diseases (contagious and not) of the canine reproductive tract can occasionally be responsible for infertility and should be investigated early in the diagnostic work-up, as contagion may be a problem in addition to the infertility. Bacterial infection such as *Brucella canis* (rarely *B. abortus* or *suis*), salmonella, streptococci and *Escherichia coli* species, viral infections (herpes, distemper, parvovirus 1 and 2) and parasitic disease (*Toxoplasma gondii* and *Neospora caninum*) have been implicated as causes of infertility in the bitch (16).

Idiopathic infertility

Physiologic processes that control folliculogenesis in the bitch are complex and involve precise, minute amounts of hypothalamic and pituitary hormones that are sensitively controlled by the ovarian feedback loop. To interrupt the hypothalamic-pituitary-ovarian axis pharmacologically usually leads to dysfunction, rather than an augmentation, of the system. The rational

administration of GnRH requires pulsatile administration, the use of GnRH analogues results in down-regulation, and the use of gonadotropins is largely unsuccessful to induce fertile estrus in known fertile bitches. There is no evidence to support the use of these hormones in bitches with a history of infertility or decreased fecundity. Careful evaluation of the underlying causes of infertility and optimal breeding management/husbandry with ovulation timing (i.e. serial evaluation of measured parameters to determine the time of ovulation) is instead recommended (1).

Summary

True infertility in the bitch must be differentiated from kennel and breeding management errors, and normal variation in the estrus cycle. The necessity of evaluation of the bitches' estrus cycle often delays completion of the infertility work-up. The confirmed diagnosis of subfertility or infertility in the bitch usually carries a poor prognosis, but management problems can usually readily be corrected resulting in normal reproduction. ♦

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