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Abnormalities in the Sexual Cycle of Bitches

Ali Risvanli, Halis Ocal and Cahit Kalkan

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Abstract

Sexual-cycle abnormalities are an important cause of infertility in bitches, with disorders such as anestrus, split estrus, and persistent estrus having varied etiologies. Sexual-cycle abnormalities in bitches may be addressed as follicular- or luteal-phase disorders. However, pet owners should have a good working knowledge of the sexual cycles of their animals in order to better understand these disorders.

Keywords: abnormality, sexual cycle, bitch

1. Introduction

Sexual-cycle abnormalities in bitches may present as anestrus, shorter, or longer cycles, as well as prolonged proestrus, prolonged estrus, split estrus, or anovulatory cycles. These cycle disorders may result from abnormal ovarian functions and are a cause of infertility [1].

1.1. Anestrus

Anestrus cycles in bitches may be either primary or secondary. If a bitch does not show signs of estrus despite having reached age of puberty, anestrus cycles are primary. The age of puberty in bitches is 6–14 months. In general, the “primary anestrus” diagnosis may be used if estrus has not occurred and the cycle has not started by 24 months of age. Although some small breeds experience first estrus at 6 months of age, cycles accompanied by estrus signs may be delayed, since the first cycles may be silent. Therefore, cycle problems are not usually investigated until a bitch reaches 2 years of age. A diagnosis of “secondary estrus” is used if estrus has not occurred for 10–18 months, although first estrus had occurred. In other words, secondary estrus is defined as the presence of a period longer than 10–18 months between

estruses. Normally, bitches experience estrus at 4–10 month (mean 6–7 months) intervals. Cycles shorter than 4 months or longer than 10 months are abnormal and can cause infertility [2–6].

Factors that lead to primary anestrus include ovariectomy or ovariohysterectomy at early age, silent heat (subestrus), abnormalities in sexual differentiation (chromosomal and genetic disorders), use of progesterone or glucocorticoids, congenital hypothyroidism, certain systemic diseases, ovarian anomalies or ovarian aplasia, progesterone-releasing ovarian cysts, and autoimmune oophoritis [2, 7].

Secondary anestrus may result from dysfunction of the thyroid gland or adrenal cortex, as well as nonendocrinological disorders, cachexia, obesity, and use of cycle-inhibiting drugs. Silent heat, luteal cysts, and some ovarian tumors may also lead to secondary anestrus as well as to primary anestrus [4, 5].

1.1.1. History of ovariohysterectomy

If taken from another person, the bitch may have been sterilized, which a new owner may overlook. Presence of a tattoo in the inguinal region and palpation or inspection of a scar from operation in the ventral wall of the abdomen may be indicators of ovariohysterectomy. However, it should be kept in mind that such a scar may be present if any intra-abdominal operation has been performed, so it may be premature to conclude that the scar resulted from ovariohysterectomy. Serum LH level measurement may be used to identify bitches that have undergone ovariohysterectomy, as serum LH is continuously high in such bitches as a result of the absence of negative feedback on LH (because the ovaries have been removed). Although elevation in serum LH provides information about ovariohysterectomy, note that this indicator may also be seen in ovarian dysfunction or during the preovulatory period (i.e., the preovulatory LH peak). Therefore, repeated measurements are required to confirm and experimental laparotomy may also be performed for a definitive diagnosis [8]. Whether ovariohysterectomy has been performed may also be detected by measuring the serum estrogen level before and 60–90 min after intravenous administration of 0.02–0.03 µg/kg buserelin. If ovariohysterectomy has been performed, estrogen levels will be found above 15–20 pg/mL.

Anti-müllerian hormone (AMH) measurement may also show whether a bitch has undergone ovariohysterectomy. AMH levels are found to be significantly lower in bitches that have undergone ovariohysterectomy compared to nonsterilized bitches [9, 10].

1.1.2. Silent heat (subestrus)

Silent heat is defined as the maintenance of ovarian functions without the presence of vulvar edema, serosanguinous vaginal discharge, and charm for male dogs. Silent heat may be observed for several cycles before first estrus in younger bitches of smaller breeds. These animals may be evaluated as “anestrus” because the pet owner may not find the external signs of estrus, or they may be identified as healthy male dogs although ovarian functions continue normally.

If silent heat is suspected, serum progesterone level should be measured once monthly in order to verify that the ovaries are functioning. A serum progesterone level above 2 ng/mL indicates functional luteal tissue. Observation of increasing superficial epithelial cells in regular vaginal cytological examinations is an indicator of functional ovaries [5].

1.1.3. Disorders of sexual development

Normal sexual development occurs in three stages: (1) chromosomal (genetic) sex development, (2) gonadal sex development, and (3) phenotypic sex development. Therefore, disorders of sex development and differentiation are classified into three matching groups: (1) sex chromosome disorders, (2) gonadal sex development disorders, and (3) phenotypic sex development disorders. All three groups of disorders result in abnormal sex differentiation and may vary in presentation between genital structure of normal and obscure appearance, and all three groups of disorders may lead to sterility or infertility [11–13].

Chromosomal analysis, anatomical and histopathological definitions of the gonads, and examination of the internal and external genitalia are required for the definite diagnosis of dogs suspected to have disorders of sexual development [11, 14].

1.1.4. Drug-related anestrus

Long-term use of some drugs, such as androgen and progestogens, causes anestrus by inhibiting cycles. Exogenous glucocorticoid administration is also reported to affect serum LH level and the normal cycle. Puberty is inhibited due to suppression of genital-canal development and ovarian activity in bitches that have undergone administration of long-acting GnRH agonists like deslorelin [15].

Similarly, cyclic activity may not be observed for a long time in prepubertal bitches that have been actively immunized against GnRH [16].

A comprehensive anamnesis should be obtained from the pet owner if drug-related anestrus is suspected; sufficient data must be obtained regarding the medical history of the bitch. If a pet owner has recently acquired the bitch and if he or she has no or insufficient information about previous vaccinations and medications, drug-related anestrus should always be considered. In such situations, the only treatment is to wait until the effects of the drug(s) disappear or until the antibody titration decreases, if immunized against GnRH.

1.1.5. Thyroid dysfunctions

There is an indirect and strict association between thyroid dysfunction and reproductivity. Hypothyroidism leads to reproductive disorders such as prolonged anestrus, silent heat, prolonged proestrus, and ovulatory problems. The prolactin level increases, which leads to impair or no development of ovarian follicles by inhibiting GnRH in bitches that have insufficient thyroid hormone release [17].

In bitches, hypothyroidism usually manifests as primary hypothyroidism, resulting from destruction of the thyroid gland. The serum total and free thyroxin levels are low in bitches

with thyroid dysfunction. Thyrotropin-releasing hormone (TRH) secretion from the hypothalamus increases due to low levels of thyroid hormones; consequently, thyroid-stimulating hormone (TSH) secretion from the pituitary gland increases. As a result of this totally physiological process, low serum total and free thyroxin levels and elevated serum TSH levels are observed in bitches with primary hypothyroidism [7].

Hypothyroidism should be kept in mind in the presence of numbness or mental fatigue, hair loss, weight increase or obesity, dryness or loss of body hair, hyperpigmentation, cold intolerance, bradycardia, high plasma cholesterol level, or anemia in a bitch with an anestrus problem. Measurement of only thyroid hormones may yield misleading or conflicting results. Therefore, a full thyroid profile should be obtained and a definitive diagnosis made in bitches suspected of hypothyroidism. For this purpose, the serum-free thyroid hormone level (particularly T₄ measurement) and the response of the thyroid gland to TSH administrations should be investigated. Furthermore, autoantibodies against thyroxin (T₄) and triiodothyronine (T₃) or thyroglobulin should be investigated in serum, as they are produced in most bitches with lymphocytic thyroiditis [7, 18, 19].

The sexual cycle may return to normal with hormone replacement therapy within 3–6 months in bitches diagnosed with hypothyroidism. For this purpose, synthetic thyroid hormone (levothyroxin) should be administered through the peroral route. A dose of 22 µg/kg b.i.d. is usually sufficient.

Although hyperthyroidism with consequent primary anestrus is a rare condition in bitches, a case has been reported in a Pinscher dog with diet-related hyperthyroidism in which primary anestrus developed; the bitch reached proestrus 13 days later after dietary regulation, with estrus then induced by cabergoline [20].

1.1.6. Pituitary gland insufficiency

The pituitary gland is important for the endocrinological functions of the adrenal glands, thyroid gland, and the ovaries. Abnormalities of the pituitary gland also negatively affect these organs. Prolonged anestrus is unusually seen in bitches with dwarfism caused by a congenital anomaly. Ovariohysterectomy is recommended in bitches that show prolonged anestrus related to pituitary gland insufficiency [6].

1.1.7. Systemic diseases

Such diseases may negatively affect reproductive function. Cycles probably will not develop if an animal is unhealthy.

1.1.8. Ovarian anomalies

Progesterone-releasing ovarian cysts, ovarian aplasia, and oophoritis may lead to primary anestrus. Definitive diagnosis can be made by histopathological examination of the ovarian tissue [21].

1.2. Approach to bitches with anestrus problems

First, it should be determined whether the pet owner has correct and sufficient knowledge of the cycle and estrous signs of bitches. The age of the bitch and whether it has experienced ovariectomy, ovariohysterectomy, or administration of any drug or vaccine (especially GnRH vaccine) should be determined. Serum progesterone level should be monitored monthly for 6–8 months before any intervention in anestrus bitches. In normal bitches, the serum progesterone level rises above 2 ng/mL within 2 months after estrus; progesterone level below 2 ng/mL for 6–8 months definitely indicates prolonged anestrus. In addition, vaginal epithelial cells should be monitored for any alterations with weekly vaginal smears.

Routine blood and urine tests (complete blood count, biochemical analysis) and thyroid function tests should be performed following general examination in anestrus bitches. Progesterone measurement and ultrasonographic examination of the ovaries should be carried out whenever luteal cyst or tumor of the ovaries is suspected. Karyotype analysis should be performed if developmental anomalies of the genital organs are suspected (such as hermaphroditism) [5].

Treatment of primary or secondary anestrus is targeted towards its etiology. No treatment is available if a bitch has undergone ovariectomy or ovariohysterectomy or in the presence of congenital sex development or differentiation anomalies, ovarian aplasia, or autoimmune oophoritis. Ovariohysterectomy is recommended for autoimmune oophoritis. Hormone replacement therapy may be administered in bitches determined to have hypothyroidism-related anestrus [22].

Estrous stimulation may be performed in anestrus bitches for which the underlying cause cannot be detected. Synthetic estrogens (diethylstilbestrol), dopamine agonists (bromocriptine and cabergoline), GnRH agonists (lutrelin, buserelin, fertirelin, deslorelin, leuprolide), or exogenous gonadotropins (LH, FSH, hCG, PMSG) may be administered for this purpose [23, 24].

Dopamine agonists are effective for stimulating fertile estrus in most bitches; however, prolonged use may be required. Bromocriptine (Parlodel, Gynodel) or cabergoline (Galastop, Dostinex) is used for this purpose. Bromocriptine is less preferred, as it causes vomiting and requires lengthy periods of administration in order to stimulate estrus. Although more expensive than bromocriptine, cabergoline may induce estruses effectively and safely with fewer side effects. Cabergoline is usually recommended at a dose of 5 µg/kg daily via the peroral route until 3–8 days after proestrus has begun [23–25].

Using GnRH and its analogs may also induce estruses. However, prolonged use for 8 days or longer or long-acting analogs such as lutrelin, deslorelin, or leuprolide is needed to induce fertile estrus. It is impractical to induce estrus by using short-acting natural GnRH or GnRH agonists, because GnRH should be given as a pulsatile continuous infusion at a dose of 0.2–0.4 µg/kg every 90 min via the intravenous or the subcutaneous route for 3–9 days. This requires 3–9 days of hospitalization and the availability of a pulsatile infusion pump. Long-acting formulations of GnRH analogs such as lutrelin, deslorelin, and leuprolide have been quite

successful when implanted subcutaneously or submucosally. Deslorelin-containing implants (Suprelorin®, 4.7 mg deslorelin) are used most frequently for this purpose [23–27].

Hypophyseal (FSH and LH) and chorionic (PMSG and hCG) gonadotropins are also used for inducing estruses. It has been found that chorionic gonadotropins are more successful than hypophyseal gonadotropins in bitches. Although various protocols have been attempted, successful results have been reported with 20 IU/kg/d PMSG applied subcutaneously for 5 days, with 500 IU intramuscular hCG on day 5. PG600, a preparation containing PMSG and hCG first produced for pigs (80 IU PMSG and 40 IU hCG/mL), is quite effective for inducing estruses [8, 28].

1.3. Recurrent estrus (shortened interestrus intervals or polyestrous)

The mean duration between estruses is 7 months (4–13 months) in bitches, and the long part of the cycle (2–10 months) comprises a mandatory anestrus phase following diestrus. In the anestrus phase, the uterus enters the involution process and the endometrium is regenerated. Anestrus shorter than 2 months naturally results in repetition of estrus at 4-month or shorter intervals, which is defined as “recurrent estrus.” It should be kept in mind that the estrous period is shorter in breeds such as the *German Shepherd Dog*, *Rottweiler*, *Basset Hound*, *Cocker Spaniel*, and *Labrador Retriever*. Fertility decreases in bitches with recurrent estrus [29] from two major causes: (1) overstimulation of the ovaries due to the formation of follicular cysts and granulosa cell tumors and (2) a premature decrease of progesterone during diestrus [21].

The period between estruses may be prolonged up to 6 months by using a weak androgen, mibolerone (Cheque Drops), recommended at a dose of 30–180 µg per day to suppress estruses [1, 30].

Furthermore, if infertility resulted from short estrous period, bitches are reported to return to normal fertility in the following cycles when estrus is suppressed with synthetic progestin administration. For this purpose, 2 mg/kg per day megestrol acetate or 0.5 mg/kg per day of chlormadinone acetate may be administered for 8 days, so administration should begin within a maximum of 3 days following the beginning of proestrus [29].

1.4. Prolonged interestrus interval

Prolonged interestrus interval is defined as an interestrus period longer than 12 months. While estrus repeats 12–13 months after the previous estrus (prolonged interestrus interval) in some adult bitches, some are not observed to experience estrus again for a long time (secondary anestrus). It should be kept in mind that the interestrus period is longer in breeds such as the *Basenji* and *Tibetan Mastiff* compared to other breeds. Secondary anestrus may result from hypothyroidism, administrations of hyperadrenocortisolism, hyperprolactinemia, progesterone-secreting ovarian cysts, progestogen, androgenic or anabolic steroid substances, systemic diseases, poor nutrition, or housing in an inappropriate environment. Thyroid function should be evaluated first in bitches with prolonged interestrus intervals. Cycles typically return to normal when the underlying cause is treated [5].

1.5. Prolonged estrus (persistent estrus)

The mean duration of estrus is 9 days in an adult dog, which may sometimes be prolonged up to 3 weeks. Estrus of longer than 21 days with the absence of ovulation at the end of this long period is defined as prolonged estrus. Prolonged estrus is related to persistent and elevated estrogen levels, which remain continuously high during the estrous phase of the cycle. This disorder is encountered frequently in younger bitches, especially during the second cycle [1].

The most important clinical signs of the continuation of estrus include cornification in vaginal epithelial cells, continuation of the desire for copulation, vulvar edema and swelling, and hyperemia in vaginal mucosa for longer than 21 days. The serum progesterone level is low, while estrogen level is high.

Persistent estruses are usually related to an estrogen-releasing source, which may be an anovulatory follicle, follicular cysts, or functional ovarian tumors (granulosa cell tumors). The follicles that develop in bitches receiving exogenous gonadotropins in order to experience estrus may sometimes lead to prolonged estruses. Exogenous estrogen administration for the treatment of urinary incontinence or vaginitis, hormone replacement therapy, and prevention of undesired pregnancy may also cause persistent estruses. Persistent estrus may also develop alongside tumors of the hypophysis or the hypothalamus or in a hepatic disease defined as portosystemic shunting in which an abnormal vascular junction is formed between the hepatic portal vein and the systemic circulation. In these cases, metabolism of estrogen in the liver is impaired.

Determination that 90% or more of the cells in a vaginal smear specimen are permanently cornified on cytological examination and nondetection of the normal increase in serum progesterone levels (remaining within the preovulatory range <2 ng/mL) indicate prolonged estrus. Detection of serum estrogen level is not a reliable method for diagnosis [1].

The first step in treatment should include a determination of the source of estrogen causing prolonged estrus. For this purpose, the ovaries should be examined ultrasonographically for the presence of abnormal structures (e.g., ovarian cyst, granulosa cell tumor); if ovarian structures cannot be identified by ultrasonographic examination, exploratory laparotomy should be performed, followed by biopsy, if required.

Follicles or follicular cysts causing prolonged estrus may heal spontaneously. If estrus is determined to last longer than 3 weeks, interventions are recommended in order to prevent bone marrow hypoplasia and/or pyometra. Treatment options should match the pet owner's expectations regarding having a puppy; if a puppy is not expected, ovariohysterectomy is the best option.

Ovulation or luteinization may be obtained by GnRH or hCG injections into follicles if the pet owner wants a puppy. hCG administration at a dose of 22 IU/kg via the intramuscular route for 3 days and GnRH (gonadorelin) administration at a dose of 10 μ g/kg via the intramuscular route for 3 days are recommended. Copulation is not recommended, as the target of these applications is not the induction of ovulation but rather the termination of the signs of prolonged estrus [1]. Ovariohysterectomy is inevitable in cases in which no response is obtained from medical applications and in prolonged estrus cases due to ovarian tumors [5].

Megestrol acetate (Ovaban, Ovarid) may be applied to reduce the signs of prolonged estrus. Low doses of megestrol acetate are recommended via the peroral route for 2 weeks. A dose of 0.1 mg/kg is proper for the first week, and a dose of 0.05 mg/kg is proper for the second week. Although progesterone treatment with megestrol acetate is effective in bitches with persistent estrus, there is the potential to trigger the development of cystic endometrial hyperplasia. Therefore, the treatment is contraindicated for bitches to be later considered for copulation. In general, ovariohysterectomy is performed within 3 weeks after treatment with progesterone in bitches with persistent estrus.

Bone-marrow suppression related to long-term estrogen toxicity may develop in bitches with persistent estrus. Nonregenerative anemia and thrombocytopenia are observed in such bitches [31]. Therefore, erythropoiesis-stimulating agents, such as synthetic erythropoietin, darbepoetin, granulocyte-colony stimulating factor, and granulocyte-macrophage colony-stimulating factor, may be used beside proper antibiotic and blood products in bitches that have anemia due to bone-marrow suppression. In addition, lithium [30, 32], synthetic anabolic steroids such as nandrolone decanoate (Deca-Durabolin), or a dihydrotestosterone derivative such as stanozolol (Winstrol) can be quite useful [33, 34].

1.6. Prolonged proestrus (persistent proestrus)

Prolonged proestrus is defined as a proestrous phase that is not followed by an estrous phase and that lasts 3 weeks or longer. In bitches with prolonged proestrus, estrus and ovulation do not occur, as the estrogen level insufficiently increases during the proestrous phase.

Prolonged hemorrhagic vaginal discharge, cornified cells higher than 50–90% on examination of vaginal smear, and serum progesterone level remaining below 2 ng/mL indicate prolonged proestrus. Treatment principles are similar to those for prolonged estrus.

1.7. Split estrus

Split estrus is a disorder in which no or quite short estrous signs develop despite the presence of proestrous signs. In this situation, pregnancy usually does not develop even if copulation occurs; the bitch is observed to enter proestrus again within 3–4 weeks. In these bitches, the next cycle is usually a normal ovulatory cycle.

Split estrus is usually seen in young bitches that have shown first estrus. However, continuous or frequent split estruses should suggest chronic premature luteolysis or hypothyroidism. Split estrus may be confused with recurrent estrus (short interestrous interval). Ovulation will not develop in dogs showing split estrus but without the typical progesterone elevation. The condition usually recovers spontaneously [1, 7].

1.8. Anovulatory cycle

A serum progesterone level not exceeding 2 ng/mL despite cytological estrous signs is defined as anovulation. Although the cell type in vaginal cytology is noncornified, diestrous-specific progesterone elevation does not occur, and the bitch enters anestrus.

The most typical signs are low serum progesterone levels and the absence of ovulation during the days after copulation in a bitch showing proestrous and estrous signs. Its incidence is about 1%. The following ovulatory cycles were observed to be normal in 45% of bitches that had an anovulatory cycle [1, 21, 35].

Thus, treatment is usually not required in bitches with an anovulatory cycle. hCG or GnRH may be administered, if desired; however, their application carries the potential to trigger pyometra [1, 21].

2. Conclusion

There are many factors leading to abnormalities in the sexual cycle of bitches. A decent anamnesis is required to find out the causes of these abnormalities. Supporting the anamnesis information by clinical and laboratory examinations is of importance for the accuracy of the diagnosis. Vaginal cytology among the diagnostic methods should be used and interpreted efficiently. Accuracy of the diagnosis forms the first step of an effective treatment. Uses of hormones, particularly gonadotropins, come into prominence in the treatment of sexual abnormalities in these animals.

Author details

Ali Risvanli*, Halis Ocal and Cahit Kalkan

*Address all correspondence to: arisvanli@firat.edu.tr

Department of Obstetrics and Gynecology, Faculty of Veterinary Medicine, University of Firat, Elazig, Turkey

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