Ovarian Remnant Syndrome

“I didn’t even know I was broken, but my nice owner is taking me tomorrow to get fixed.”

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Ovarian Remnant Syndrome

- Definition
- Incidence
- Clinically applicable anatomy and etiology
- Clinical presentation
- Differential diagnoses
- Diagnostic evaluation
  - Cytological evaluation
  - Endocrine assays
  - Imaging
- Resolution
Ovarian Remnant Syndrome

• Failure to remove some or all ovarian tissue at the time of surgical sterilization
  – Cyclic hormonal profile associated with proestrus, estrus
  – Demonstration of physical and behavioral signs
  – Predisposition to diseases of the luteal phase if uterine tissue also remains
Incidence

• Very common amongst complications of ovariohysterectomy (17-43%)

• Retrospective analyses vary in findings
  – Most: queen > bitch
  – Few: bitch > queen (canine case demographics?)

• Bitch
  – Large breeds over-represented
  – Right >>> left ovary due to more cranial location, particularly in deep-chested breeds
Etiology of Retained Ovarian Tissue

• Surgical error resulting in entire ovary/ovaries not being removed
  – Bitch > queen
  – Small incision site → inadequate exposure, particularly in obese bitches
  – Complete ovarian bursa in bitch vs. relatively exposed ovary in queen

• Auto-transplantation of fragment of ovary during removal
  – Queen > bitch
  – Fragmentation of exposed ovary → fragment attaches to mesentery → re-vascularization

• “Supranumerary” or “ectopic” ovaries
  – Reported in queens, but RARE
Clinical Signs

• Canine: consistent with proestrus, estrus
  – Vulvar swelling
  – Attraction of male dogs, demonstration of breeding reflexes
  – Serosanguinuous vulvar discharge if uterine tissue remains
  – Cyclic or continuous (neoplasia)

• Queen: consistent with follicular phase
  – Receptivity: crouching, lordosis, vocalization, head rubbing, treading
  – +/- Allowing mating
Clinical Signs

• Less common clinical signs associated with luteal phase
  – Pseudocyesis
  – Stump pyometra
• Time to onset variable (averages)
  – Canine
    • 12 months if no neoplasia of remnant tissue
    • 96 months if remnant became neoplastic
  – Feline
    • Highly variable: 17 days – 9 years!!!
Differential Diagnosis
Serosanguinuous Vulvar Discharge

- Urinary tract infection
- Exposure to exogenous estrogens
- Ovarian remnant that has undergone transformation to a granulosa (theca) cell tumor
- Less common causes
  - Vaginal/vestibular masses, e.g., transitional cell carcinoma
  - Suture granuloma
  - Infection of uterine/cervical stump in absence of ORS
  - Coagulopathy
  - Increased adrenal estrogen production???
Utility of various diagnostic modalities varies by presence/absence of clinical signs of estrogenization at time of presentation

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<th>Diagnostic Modality</th>
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<td>Breeding reflexes</td>
<td>Yes</td>
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<td>Vaginal cytology</td>
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<tr>
<td>[Progesterone]_serum</td>
<td>Maybe</td>
<td>Maybe</td>
</tr>
<tr>
<td>[LH]_serum</td>
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<td>Mostly</td>
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<tr>
<td>[AMH]_serum</td>
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<td>Yes</td>
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<td>[Estradiol]_serum</td>
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<tr>
<td>Transabdominal ultrasonography</td>
<td>Maybe</td>
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Canine Estrous Cycle
Feline Estrous Cycle

Non-pregnant luteal period of 30-35 days
Diagnosis
Breeding Reflexes

• Confirms estrogenization

• Timing
  – Bitch
    • Must be in proestrus or estrus, based upon ovarian status
    • Vulvar swelling, but discharge need not be present
    • Tail flagging, vulvar lift, lordosis
  – Queen
    • Must be during physiologic breeding season if indoor/outdoor cat
    • Must be during follicular phase
Diagnosis
Breeding Reflexes

- Tail flagging
- Vulvar lift (pouting)
- Lordosis
Diagnosis
Vaginal Cytology

• Procedure
Diagnosis
Vaginal Cytology

• Confirms estrogenization in both bitch and queen
  – Best performed when clinical signs evident
  – Does not definitively diagnose or rule out ovarian remnant
  – Other potential sources of estrogen
    • Intentional administration of DES or estriol for treatment of urinary incontinence (bitch)
    • Exposure to human estrogen creams
    • Certain feedstuffs and nutraceuticals, e.g., flaxseed

ORS in anestrus; spayed
ORS in proestrus or estrus; other estrogen source
Diagnosis

Serum Estrogen Concentration

- Serum estradiol concentration
  - Single sample may be inadequate, as serum estrogen concentration basal during much of the cycle
  - > 15 pg/ml (> 20 pg/mL in queen) suggestive of, but not specific for, follicular activity
  - Depending upon assay, will be increased in cases of inadvertent exposure and intentional administration of exogenous estrogens
  - Not routinely performed
Diagnosis
Serum Progesterone Concentration

• Progesterone concentration above basal confirms presence of ovarian tissue in both bitch and queen
  – \([\text{Progesterone}]_{\text{serum}} \geq 2.0 \text{ ng/mL}\) must be of luteal origin
  – Adrenal gland will not produce progesterone in such large amounts
• Absence of serum progesterone ≠ absence of ovarian tissue
  – Bitch in anestrus or proestrus
  – Queen that has not been induced to ovulate during previous month
• May be used to confirm that follicles have ovulated → CLs will be visible on remnant → helpful in locating remnant at surgery
Diagnosis
Serum Progesterone Concentration

• Timing of measurement
  – Bitch
    • 2-4 weeks from onset of clinical signs of heat
    • 5-7 days following induction of ovulation
      – Human chorionic gonadotropin (hCG), 500-1000/dog IU, IM once
      – GnRH analog, 2.0 μg/kg, IM or IV, once
      – Not all ovarian remnants respond to pharmacologic stimulation
Diagnosis
Serum Progesterone Concentration

• Timing of measurement
  - Queen MUST BE INDUCED TO OVULATE
    • Mechanical vaginal stimulation using swab 3-6 times over 1 hour
    • Pharmacologic induction: 25 μg GnRH analog IM during behavioral estrus
    • Measure \([\text{progesterone}]_{\text{serum}}\) 2-3 weeks later
Diagnosis

Serum LH Concentration

- Spayed → removal of negative feedback on hypothalamus from ovarian steroid hormones → ↑↑↑↑ GnRH → ↑↑↑↑ LH, ↑↑↑↑ FSH
  - \([LH]_{\text{serum}} \geq 8.0 \text{ ng/mL} \) in spayed bitches
  - \([FSH]_{\text{serum}} \) 12x higher in ovariectomized bitches
- \([FSH]_{\text{serum}} \) measurement not commercially available
- \([LH]_{\text{serum}} \) measurement readily available
  - Commercial labs provide quantitative results
  - Witness® LH
    - Qualitative bitch/queen-side test
    - Threshold for positive result at 1 ng/mL (equivocal)
    - Results must be interpreted in conjunction with history and clinical signs
Diagnosis
Serum LH Concentration

- Ovarian remnant → at least some negative feedback →
  - ↑↑↑↑ LH at the LH surge in bitch and just following mating in queen
  - False positive results possible, therefore, BUT…
  - Clinical signs of estrus should be apparent in both species at that time
Diagnosis

Serum LH Concentration

- Equivocal results may occur with a single test
  - Negative result (low [LH]_{serum}) 98% sensitive, i.e., highly accurate in detecting bitches WITH ovarian tissue
  - Specificity moderate (78%) in that single high [LH]_{serum} not a reliable indicator that ovaries had been removed
    - Overlap between [LH]_{serum} in bitches with ovaries completely removed and anestrous bitches with ovarian tissue during pulsatile LH release episodes
    - Consider history in interpreting results
    - Re-test at least once more, 2 hours later
      - Negative result → bitch has ovarian tissue
      - 3 additional positive results → bitch is completely ovariectomized
Diagnosis

Serum AMH Concentration

- Anti-Müllerian hormone
  - Causes regression of the (female) paramesonephric ducts in the male fetus
  - In the female, produced constitutively by granulosa cells of primary, secondary, and early antral follicles AFTER development of the tubular tract
- Manufactured exclusively by granulosa cells → specific for the presence of ovarian tissue
Diagnosis
Serum AMH Concentration

• Identifies presence/absence of ovarian tissue accurately at any time during the estrous cycle
  – Females > 6 months of age
  – Sensitivity: 93.9%
  – Specificity: 93.8%

• Spaychek®
  – Single serum sample
  – Qualitative test kit
  – Offered through laboratories at various academic institutions
    • University of Missouri
    • University of California at Davis
Diagnosis
Transabdominal Ultrasonography

• Value
  – Most useful as an adjunct to locate remnant(s) to be removed at surgery after confirmation of diagnosis via vaginal cytology and/or endocrine testing
  – Assessment for presence of uterine stump

• Limitations
  – Identifies the presence/location of retained ovarian tissue in only 50-75% of cases
  – May be challenging to differentiate remnant from suture granuloma at pedicle
Benign (?) Neglect

• Possible sequelae
  – Pyometra of the uterine stump (if present)
  – Transformation of the remnant to a granulosa (theca) cell tumor (5-30%)
    • 23.8% in ovarian remnant bitches versus 6.25% in normal intact bitches
  – Potential for increased risk of mammary neoplasia (if spayed prior to third heat)
  – Persistence of undesirable behavior and clinical signs
Treatment

• Laparotomy or laparoscopy
  – Often times referred
  – Removal of ovarian tissue and any remaining uterus
  – Facilitated by the presence of follicle(s), but especially of CLs
  – +/- Histopathology to confirm excised tissue to be ovarian

• Prognosis
  – Excellent
  – Majority of GCTs (~70%) do not metastasize
Questions?