Reproductive Endocrine Testing and Exogenous Hormone Therapy in Equine Practice

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Reproductive Endocrine Testing
Diagnostic Applications

• Highly useful
  – Cryptorchidism
  – Granulosa-theca cell tumor
  – Pregnancy diagnosis

• Moderately useful
  – High risk pregnancy assessment and monitoring

• Not at all useful
  – Subfertility in the stallion
Cryptorchidism
Indications for Evaluation

• Previously “gelded” horse
  – “Studdish” behavior
  – Poor trainability

• Risk for development of malignant neoplasia
  VERY LOW!
  – Teratoma may occur in abdominally-retained testis
  – May cause colic
Normal Descent of the Testes

- Testes usually descend into scrotum between 30 days prior to and 10 days after birth.
- Descent of inguinally retained testes may be completed as late as 9 months of age, but this is NOT normal!
Cryptorchidism

- **Mechanisms of development**
  - Physical or mechanical abnormalities
    - Abnormal or insufficient development of the gubernaculum
    - Inadequate development of the epididymal tail → failure to dilate internal inguinal ring
    - Insufficient intra-abdominal pressure to distend vaginal process
    - Testicular teratoma
  - Aberrations of the reproductive hormonal environment
    - ↓ Insulin-like peptide 3
    - ↓ Testosterone
    - ↓ Receptors for ILP-3, testosterone
Cryptorchidism in the Horse

- **Unilateral retention**
  - Subcutaneous tissue
  - Inguinal canal
  - Abdomen
    - Left testis more frequently retained

- **Bilateral retention**
  - Both testes abdominally retained or both testes inguinally retained
  - Mixed intra-abdominal, inguinal retention uncommon

Diagnostic Evaluation

• Definitive castration history most often unavailable

• Goals
  – Confirm presence of functional testicular tissue
  – Locate occult gonad
Diagnostic Evaluation
Physical Examination

• Palpation of scrotal contents and superficial inguinal area
  – Purpose
    • Confirm absence of scrotal testis
    • Identify testis at superficial aspect of the inguinal canal
  – Sedation using $\alpha_2$-agonist tranquilizer beneficial

NOT ACEPROMAZINE!!!
Diagnostic Evaluation
Physical Examination

- Palpation per rectum
  - Testis in deeper aspect of inguinal canal
    - Ductus deferens palpable entering internal inguinal ring
  - Intra-abdominally retained testis
    - Epididymal tail +/- testis often identifiable in area of internal inguinal ring
Diagnostic Evaluation
Imaging Studies

- Transrectal ultrasonography confirms presence of abdominally-retained testis identified by palpation
- Transabdominal ultrasonography from inguinal region to flank
- Poor screening tests
  - Require some experience with procedures and image recognition
  - Time-consuming
Diagnostic Evaluation

Endocrine Assays

• Testosterone
  – Baseline
  – Stimulated response

• Anti-Müllerian hormone

• (Estrone sulfate)

• (Inhibin)

• (Urinary sex steroids)
Endocrine Assays: Baseline Testosterone

- $[T]_{serum} < 100\text{-}250\ \text{pg/mL} \rightarrow \text{NO testicular tissue (exact values dependent upon lab)}$

- Equivocal results in 14%*

  - Age
    - Intact colts < 18 months may have baseline $[T]_{serum}$ in this range
    - Cryptorchid horses > 9 years may have very low resting $[T]_{serum}$ **

  - Season
    - Borderline low $[T]_{serum}$ possible in the autumn**

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Endocrine Assays: hCG Stimulation Test

**Diagnostic Evaluation**

- **$T_0$**
  - hCG
  - LH-like activity

- \[ [T]_{serum} \uparrow \uparrow \]

- Measure $[T]_{serum}$

- \( (T_1), (T_2), (T_3), (T_{24}), (T_{48}), (T_{72}) \)

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Fig. 8-5. Synthesis and production of testosterone by the Leydig cell. (Adapted from: A. H. Payne and G. I., Youngblood, Biol. Reprod., 52:217, 1995.)
Diagnostic Evaluation

Endocrine Assays: hCG Stimulation Test

• hCG Stimulation Test
  - \[ [T]_{\text{serum}} > 2-3 \text{ times baseline} \rightarrow \text{PRESENCE of testicular tissue} \]
  - Increased diagnostic value over measurement of baseline concentration alone
    • Very high sensitivity (97%), moderate specificity (76%)*
    • Equivocal results in 6.7%*
  - In rare cases, stimulation may require as long as 72 hours after hCG administration

Diagnostic Evaluation

Endocrine Assays: Estrone Sulfate

- Estrone sulfate
  - Leydig cells
    - Produce estrone in quantities > testosterone
    - Conjugation → water soluble, inactive → blood vessels
  - Single serum sample
  - Horses > 3 years of age
Diagnostic Evaluation

Endocrine Assays: Estrone Sulfate

- Estrone sulfate
  - High sensitivity (87%), moderate specificity (77%)*
  - Measurement of estrone sulfate is no longer diagnostic test of choice
  - NOT applicable to donkey jacks

Diagnostic Evaluation

Endocrine Assays:

Anti-Müllerian Hormone (AMH)

- Glycoprotein secreted by Sertoli cells in large quantities from time of fetal sexual differentiation through onset of puberty
  - Regression of Müllerian (paramesonephric ducts) in male fetus, suppression of Leydig cell differentiation and steroidogenesis until puberty
  - Produced exclusively by the testis, rendering it sensitive and specific

- $\downarrow[\text{AMH}]_{\text{serum}}$ during and after puberty in normal stallions
  - Formation of the blood-testis barrier at puberty $\rightarrow$ AMH secreted into seminiferous tubule lumen $\rightarrow$ seminal plasma
  - Decrease in production


Diagnostic Evaluation
Endocrine Assays:
Anti-Müllerian Hormone (AMH)

- Produced in large quantities in cryptorchid testes, Sertoli cell tumors and intersex gonads*
  - Cryptorchid testes retain some markers of immaturity at cellular and mRNA levels**
    - Failure of Sertoli cells to mature and arrest proliferation
      - ↑ [AMH]
      - ↑ [AMHR2]
      - ↓ [CDKN1B]
      - ↓ [AR]
    - Impaired Leydig cell function → ↓ [T]
  - Expressed constitutively
  - No stimulation or serial measurements required


Diagnostic Evaluation

Endocrine Assays:

Anti-Müllerian Hormone (AMH)

• Absolute differences in $[\text{AMH}]_{\text{serum}}$ statistically significant between stallions, geldings and cryptorchid equines*
  
  – Geldings: $0.07 \pm 0.01$ ng/mL
  – Stallions: $14.7 \pm 2.4$ ng/mL
  – Cryptorchids: $32.4 \pm 5.0$ ng/mL
  – Little sensitivity and specificity data, but in theory, both should be high!

Diagnostic Evaluation

Endocrine Assays:

Anti-Müllerian Hormone (AMH)

- Available through UC Davis Veterinary Endocrinology Lab
  - Cryptorchid $[\text{AMH}]_{\text{serum}} > 15$ ng/mL
  - 2 mL serum on ice pack
  - ELISA test run weekly
  - Cost
    - $[\text{AMH}]$ only: $60$
    - $[\text{AMH}]$ and $[\text{Testosterone}]$ (Cryptorchid Panel): $75$
  - No reason to believe that it will not work in donkeys, mules
  - Interesting seasonal variation in stallions, but of little to no relevance when diagnosing cryptorchidism*
    - Peak: May, ~26 ng/mL
    - Nadir: November, ~16 ng/mL

Diagnostic Evaluation
Endocrine Assays:
Urinary Sex Steroids

• Adapted from racing industry testing for banned performance enhancing anabolic steroids

• Advantages
  – Noninvasive
  – Single urine sample
  – “Induction” not required

• Horses ≥ 2 years of age

Diagnostic Evaluation
Endocrine Assays: Urinary Sex Steroids

- Identified steroid markers, the concentrations of which did not differ between intact stallions and cryptorchid equines (overall N=5000)
  - Testosterone not useful alone, as adrenal gland contributes in geldings
  - 5(10)-Estrone-3β, 17α-diol most specific, particularly when measured in conjunction with ↑ testosterone
  - Correctly identified 18/18 cryptorchid males later confirmed at surgery or post-mortem

Endocrine Testing for Cryptorchidism
Take Home Points

✓ Physical examination and imaging studies may contribute to the diagnosis of cryptorchidism; however, endocrine assays are usually required to confirm the diagnosis.

✓ Use of the hCG stimulation test increases accuracy of diagnosis over measurement of baseline serum testosterone concentration alone.

✓ Measurement of serum [AMH] alone or in concert with [testosterone] appears to be useful in diagnosing cryptorchidism and is likely to replace measurement of baseline and stimulated [testosterone].
Granulosa (Theca) Cell Tumors
The Problem of Over-Diagnosis

Alterations in (sexual) behavior

Palpation of “enlarged” ovary

DIAGNOSIS: Granulosa Cell Tumor → Refer for ovariectomy
Pathophysiologic Behavior of the Granulosa-Theca Cell Tumor

[Diagram showing the biochemical processes involved in the behavior of granulosa-theca cell tumors, including the roles of LH, FSH, cAMP, testosterone, and inhibin.]
Pathophysiologic Behavior of the Granulosa-Theca Cell Tumor
Pathophysiologic Behavior of the Granulosa-Theca Cell Tumor

Antral Follicle

Theca interna cell

Granulosal cell

Cholesterol

Testosterone

Protein kinase

cAMP

FSH

LH

Blood

Estradiol (E2)

Protein kinase

Aromatase

Estradiol (E2)

Inhibin

Capillary

Blood
Pathophysiologic Behavior of the Granulosa-Theca Cell Tumor
Granulosa-Theca Cell Tumors
Diagnostic Evaluation

Alterations in (sexual) behavior

Palpation of “enlarged” ovary

Additional physical examination and palpation findings

Transrectal ultrasound imaging

Reproductive hormone analysis

DIAGNOSIS: Granulosa Cell Tumor → Refer for ovariectomy
Granulosa-Theca Cell Tumors
Diagnostic Evaluation

Alterations in (sexual) behavior

DIAGNOSIS: Granulosa Cell Tumor → Refer for ovariectomy
Granulosa-Theca Cell Tumors
Diagnostic Evaluation

History

- "Stallion-like" behavior
  - Herding
  - Mounting
  - Virile vocalization
  - Stud pile deposition
- Virilization
- Continuous estrus
  - Estrus at inappropriate intervals
- Failure to demonstrate estrus
- Infertility

Virilization 46%
Nymphomania 22%
Anestrus 32%
Granulosa-Theca Cell Tumors
Diagnostic Evaluation

Alterations in (sexual) behavior

Palpation of “enlarged” ovary

Additional physical examination and palpation findings

DIAGNOSIS: Granulosa Cell Tumor → Refer for ovariectomy
Granulosa-Theca Cell Tumors
Diagnostic Evaluation
Palpation Per Rectum

- Unilateral ovarian enlargement
  - 10-20 cm in diameter
  - Firm to hard consistency
  - OVULATION FOSSA OBLITERATED!!!
  - Pain not commonly elicited
- Contralateral ovary small and inactive
Granulosa-Theca Cell Tumors

Diagnostic Evaluation

- Alterations in (sexual) behavior
- Palpation of "enlarged" ovary
- Additional physical examination and palpation findings
- Transrectal ultrasonography

**DIAGNOSIS:** Granulosa Cell Tumor → Refer for ovariectomy
Granulosa-Theca Cell Tumors
Diagnostic Evaluation
Transrectal Ultrasonography

- Affected ovary
  - Multicystic appearance
  - Hypo- to hyperechoic stroma
  - Thickened tunica albuginea
  - +/- Hemorrhage +/- clot

- Contralateral ovary
  - Small
  - ↑ Inhibin → FSH-dependent follicular growth halted → absence of endocrinologically active follicles
Granulosa-Theca Cell Tumors
Diagnostic Evaluation

Alterations in (sexual) behavior

Palpation of “enlarged” ovary

Additional physical examination and palpation findings

Transrectal ultrasound imaging

Reproductive hormone analysis

DIAGNOSIS: Granulosa Cell Tumor → Refer for ovariectomy
Granulosa-Theca Cell Tumors
Diagnostic Evaluation
Endocrine Assays

- Testosterone
- Inhibin
- Progesterone
- Anti-Müllerian Hormone (AMH)
- Estradiol
- MicroRNAs
Granulosa-Theca Cell Tumors
Diagnostic Evaluation
Endocrine Assays

- Testosterone
- Inhibin
- Progesterone
- AMH
Granulosa-Theca Cell Tumors
Diagnostic Evaluation
Endocrine Assays

- $[\text{Testosterone}]_{\text{serum}}$: Increased in 40-60% of affected mares
- $[\text{Inhibin}]_{\text{serum}}$: Increased above normally cycling mares in 87-95% of mares with GCTs
- $[\text{Progesterone}]_{\text{serum}}$: Basal (<1.0 ng/mL) in most affected mares

**BOTTOM LINE:** Considering increased serum inhibin and/or testosterone concentrations, **84-95%** of mares affected by GCTs may be diagnosed using the “GCT Panel”.
Granulosa-Theca Cell Tumors
Diagnostic Evaluation
Endocrine Assays

• Equivocal cases with $[\text{Progesterone}]_{\text{serum}} \geq 1.0 \text{ ng/mL}$
  – Non-pregnant mares
    • $[\text{Testosterone}]_{\text{serum}}$ and $[\text{Inhibin}]_{\text{serum}}$ tend to be equivocal
    • Approximately 50% confirmed with GCT by alternate test
  – Pregnant mares
    • $[\text{Testosterone}]_{\text{serum}}$ and $[\text{Inhibin}]_{\text{serum}}$ may be increased above reference range in absence of GCT
    • Confounds diagnosis of GCT
    • Alternate testing required

Granulosa-Theca Cell Tumors
Diagnostic Evaluation
Endocrine Assays

- Anti-Müllerian hormone (AMH) present in low concentrations in normal mares
  - Small antral follicles
  - [AMH] does not change significantly with stage of cycle or pregnancy
- In cases with GCT confirmed by histopathology [AMH]_{serum} is increased*
  - Normal cyclic mares: 0.96 +/- 0.08 ng/mL
  - Pregnant mares: 0.72 +/- 0.05 ng/mL
  - GCT mares: 1901.4 +/- 1144.6 ng/mL
- [AMH]_{serum} ≥ 4.0 ng/mL appears to be diagnostic for GCT**


Granulosa-Theca Cell Tumors
Diagnostic Evaluation
Endocrine Assays

• Improved sensitivity**
  • $[\text{AMH}]_{\text{serum}}$ 98% > $[\text{inhibin}]_{\text{serum}}$ 80% > $[\text{testosterone}]_{\text{serum}}$ 48%
  • $[\text{AMH}]_{\text{serum}}$ 98% > $[\text{inhibin}]_{\text{serum}}$ in combination with $[\text{testosterone}]_{\text{serum}}$ 84%
• $[\text{AMH}]_{\text{serum}}$ appears to rise earlier than other markers, e.g., inhibin, allowing for earlier diagnosis

• Commercially available tests from UC Davis
  • GCT Panel ([inhibin], [testosterone], [progesterone]): $90
  • [AMH], [inhibin],[testosterone]: $130
  • [AMH], [inhibin]: $100
  • [AMH]: $60

Granulosa-Theca Cell Tumors
Diagnostic Evaluation
Histopathological Confirmation

Definitive diagnosis requires histopathological evaluation!

[AMH] ↓ rapidly into range for normal cyclic mares within 2 weeks or less of removal of affected ovary

Granulosa-Theca Cell Tumors
Ruling Out Differential Diagnoses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Endocrinological Activity?</th>
<th>Contralateral Ovary Size</th>
<th>Ultrasonographic and/or Gross Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulosa-theca cell tumor</td>
<td><strong>YES</strong> <em>(various)</em></td>
<td><strong>SMALL</strong></td>
<td></td>
</tr>
<tr>
<td>Ovarian hematoma</td>
<td>No</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Anovulatory hemorrhagic follicle</td>
<td>Yes <em>(P₄)</em></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Normal ovary during vernal transition</td>
<td>Yes <em>(E₂)</em></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Neoplasms other than GCT</td>
<td>No</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>
Granulosa-Theca Cell Tumors
Take Home Points

✓ Although the GTCT constitutes the most common ovarian neoplasm in the mare, the condition tends to be over-diagnosed.

✓ While only approximately one half of mares suffering from GTCTs exhibit “stallion-like” behavior, all affected mares demonstrate abnormal estrous cyclicity.

✓ Accuracy of diagnosis is maximized using reproductive hormone analysis, e.g., measurement of serum concentrations of AMH, inhibin, testosterone and progesterone.

✓ In no other condition producing unilateral ovarian enlargement is endocrinologic activity present that mediates both down-regulation of the contralateral ovary and persistent abnormal sexual behavior.
The Pregnant Mare
Reproductive Endocrine Testing
The Brood Mare

• Pregnancy diagnosis
• Monitoring the “well-being” of the pregnancy
• Guidance of exogenous hormone therapy
Reproductive Endocrine Testing
Pregnancy Diagnosis

• Useful in cases where palpation and ultrasonography per rectum are physically impossible or otherwise unsafe
  – Miniature mares
  – Severely intractable animals
  – Client preference
Reproductive Endocrine Testing
Pregnancy Diagnosis

- Exploit endocrine profile of pregnant mare
  - Measure pregnancy-specific proteins and hormones
  - Clinical utility of endocrine products as indicators of pregnancy varies by stage of gestation
Reproductive Endocrine Testing

Pregnancy Diagnosis < 45 days

- Pregnancy maintained by progesterone secreted by primary CL
- Endocrine testing to confirm live embryo/fetus not sensitive, i.e., measurement of $[P4]_{\text{serum}}$ is NOT diagnostic!!!
- No pregnancy-specific substance before ~ 45 days
Reproductive Endocrine Testing

Pregnancy Diagnosis 45-110 days

- Pregnancy maintained by multiple progestin sources
  - Primary CL → P4
  - Endometrial cups → equine chorionic gonadotropin (eCG) → accessory CLs → P4
  - Steroid precursors from fetal gonad → fetoplacental unit → 5α-pregnanes
Reproductive Endocrine Testing
Pregnancy Diagnosis: eCG

- Pregnancy-specific protein
- \([\text{eCG}]_{\text{serum}}\) profile
  - Begins to rise at 35-42 days post-ovulation
  - Peaks at 55-60 days
  - Gradually declines to nondetectable levels by 120-150 days
- Serum concentrations best measured between 45-90 days

Source: Buergelt CD. Color Atlas of Reproductive Pathology of Domestic Animals
Reproductive Endocrine Testing

Pregnancy Diagnosis: eCG

• Highly sensitive
  – ~ 90%
  – False positive if pregnancy loss subsequent to cup formation

• Highly specific
  – ~ 95%
  – False negatives
    ▪ Assay performed outside optimal window
    ▪ Mares carrying mule fetuses (false negatives to 81%)
Reproductive Endocrine Testing
Pregnancy Diagnosis: Estrone Sulfate

- Assays to measure $5\alpha$-pregnanes, relaxin not commercially available
- Steroid precursors from fetal adrenal glands → fetoplacental unit → vast amounts of estrogens, principally, estrone sulfate
Reproductive Endocrine Testing

Pregnancy Diagnosis: Estrone Sulfate

- Measurement of $[\text{estrone sulfate}]_{\text{serum}}$ widely available
  - May be measured in standard-sized mares as early as 45 days: > 6 ng/mL
- Estrone sulfate > 100 ng/mL indicative of live fetus in mid-late gestation
Reproductive Endocrine Testing
Pregnancy Diagnosis: Estrone Sulfate

- Valid to confirm pregnancy in horse and miniature mares as well as jennies beginning at ~ 80 days
- $[\text{Estrone sulfate}] > 60 \text{ ng/mL}$ in miniature mares pregnant > 80 days
- False negative results if $[\text{estrone sulfate}]_{\text{serum}}$ measured < day 80
Reproductive Endocrine Testing

Pregnancy Diagnosis: Disadvantages

- Unable to definitively diagnose pregnancy prior to 45 days using [eCG] and/or [estrone sulfate]
- Measurement of [eCG] and/or [estrone sulfate] limited to confirmation of pregnancy
  - Cannot differentiate singleton vs. twin pregnancy
The Pregnant Mare

- Monitoring the “well-being” of the pregnancy
- Guidance of exogenous hormone therapy
Reproductive Endocrine Testing
Problem Mares Suffering Early Embryonic Death

- Measurement of $[P4]_{\text{serum}}$ becoming somewhat routine at initial examination for pregnancy
- Significance of decreased $[P4]_{\text{serum}}$ controversial
  - Primary luteal insufficiency and failure extremely rare
  - Decreased $[P4]_{\text{serum}}$ most often found in association with endometritis
Exogenous Hormone Supplementation
Days 0-40

• Supplementation at <2.5-4.0 ng/mL, depending upon source/lab

• Beneficial
  – Mares at risk for failure of maternal recognition of pregnancy (large cysts, ventral uterine sacculations)
  – Mares at risk for luteolysis after maternal recognition of pregnancy (fever, septicemia)

• Not beneficial
  – Endometritis (CONTRAINDICATED!!!)
Exogenous Hormone Supplementation
Efficacious Products

- **Regu-Mate®** (altrenogest)
  - Labeled for use in horses, but **not** pregnant mares
  - 0.044 mg/kg PO q24h (1 mL per 110 pounds PO q24h)
  - Lacks cross-reactivity with progesterone in serum assays, allows for monitoring of [progesterone]

- **Altresyn®** (altrenogest)
  - Relatively new FDA-approved generic formulation
  - Same concentration and dosing as Regu-Mate®
  - ~20% less expensive than Regu-Mate®
Exogenous Hormone Supplementation

**Efficacious Products**

- **Progesterone in oil**
  - Compounded
  - **Short-acting:** 150 mg IM q24h
    - Immediate return to estrus possible upon withdraw*
  - **Long-acting:** 1500 mg IM q7-10d
    - Return to estrus delayed until depot product metabolized
  - Injection site reactions and muscle soreness possible
  - Treatment of choice in NPO colic cases
Exogenous Hormone Supplementation

Primary CL

Betla P4-D10

P in oil

Minimum concentration

October
Exogenous Hormone Supplementation
Ineffective Products

- Norgestomet implants
- Progesterone and estradiol implants
- Medroxyprogesterone acetate (Depo Provera®)
- Melengesterol acetate
- Hydroxyprogesterone caproate
Exogenous Hormone Supplementation Days 40-100

- Many sources of progestagen
  - Progesterone
    - Primary CL
    - Accessory CLs of varying ages (some < 5 days and refractory to PGF$_{2\alpha}$)
  - $5\alpha$-Pregnanes: increasing contribution but not yet sufficient alone
- Pregnancy virtually indestructible
- Progestin therapy scientifically dubious, but routinely practiced
Exogenous Hormone Supplementation
Days 100-180

• Sources of progestagen
  – Progesterone from aCLs
    ▪ Present early, but unnecessary
    ▪ Bilateral ovariectomy may be performed ≥ 150 days → pregnancy carried to term
  – 5α-Pregnanes
    ▪ Concentrations sufficient to maintain pregnancy alone

• Progestin therapy scientifically dubious, but often practiced
Exogenous Hormone Supplementation
Days 180-Term

• Only 5α-pregnanes maintain pregnancy
  • Measurement of $[P4]_{\text{serum}}$ is irrational, as it will be quite low in normal mares
  • Supplementation based upon low $[P4]_{\text{serum}}$ is therefore irrational as $[P4]_{\text{serum}}$ does not increase until just prior to parturition in the normal mare
Exogenous Hormone Supplementation
The Pregnant Mare with Colic

- **0-40 days gestation**
  - Initiate therapy IMMEDIATELY to prevent pregnancy loss in the face of potential luteolysis
  - Re-evaluate pregnancy and CL/[progesterone] at one week
    - If live embryo and normal CL detected, wean off therapy by 20%/day
    - If live embryo and no CL, continue therapy at least until aCLs formed; measure [progesterone]
    - If not pregnant, discontinue therapy
Exogenous Hormone Supplementation
The Pregnant Mare with Colic

• Injectable, short-acting progesterone formulation
  – Absorption more predictable than oral formulation in mares suffering from colic
  – If EED occurs before ~35 days, withdrawal of therapy allows for immediate return to estrus
Exogenous Hormone Supplementation
The Pregnant Mare with Colic

- 40+ days gestation
  - Not so rational, but routinely performed
    - “Double-dose” protocols common, with weaning to single dose one week following end of “insult”
    - Use of long-acting preparations advisable only after documentation of live fetus following full recovery of mare
  - Wean off beginning at ~30 days prior to expected foaling date, reducing dose by 20% every second day
    - Mare will “foal through” altrenogest administration BUT
    - Continued administration results in prolonged stage II, lower neonatal respiratory rate, decreased neonatal viability
  - But, it does no harm, right?
Exogenous Hormone Supplementation
The Pregnant Mare with Colic

- Mare may still abort
- Increased risk for complications
  - Delayed fetal expulsion due to cervical closure?
  - Dystocia?
  - Retained fetal membranes?
  - Metritis?
Exogenous Hormone Supplementation
High Risk Pregnancies

- Pregnancy maintained exclusively by $5\alpha$-pregnanes from 180 days
  - Only severe maternal disease or significant direct fetal and/or placental disease compromise production to the point that pregnancy is jeopardized
  - Can a placenta that produces insufficient progestagens for maintenance of pregnancy sustain fetal health and growth in every other respect?
Reproductive Endocrine Testing
High Risk Pregnancies

- Measurement of serum [estrogens] and [progestins] as indicators of fetal “viability”
- Hypothesis: compromised fetoplacental unit produces ↓ estrogens and ↑ progestins → profile mimics that just prior to mare starting parturition
- [Progestin] then plummets precipitously; thus, the rationale for supplementation
Reproductive Endocrine Testing
High Risk Pregnancies

• Placentitis
  – Serum [relaxin] decreased in compromised pregnancies*
    • Profile varies by breed
    • Inconsistencies in profiles post-treatment
    • Not routinely utilized
  – Serum [estrogens] < 1000 pg/mL
    • [Estrone sulfate] remains unchanged
    • [17β-estradiol sulfate] dramatically decreases**
  – Serum [progestins] markedly increased

Reproductive Endocrine Testing
High Risk Pregnancies

• Placentitis
  – [Serum amyloid A]*
    • ↑ 120 h prior to parturition in normal mares
    • Experimental intra-cervical inoculation→ ↑ 48-144 h, but preceded by clinical disease by 24 h
    • Treated mares do not experience ↑
    • Nonspecific
  – [Haptoglobin] rapidly, dramatically increased, but also nonspecific**

Reproductive Endocrine Testing
High Risk Pregnancies

• Placentitis
  – Adjunct to ultrasonographic evaluation of utero-placental unit thickness monitoring
    • Measurement of [P4] and transrectal ultrasonography identified 20/22 experimentally induced cases*
  – Reduction in usage of prophylactic pulsatile antimicrobial administration in “at risk” mares

* Bailey CS. Update on placentitis—what has been accomplished in the last 3 years? Clin Therio 2013; 5:326-333.
Exogenous Hormone Supplementation
High Risk Pregnancies

• Controversial
  – Some advocate supplementation with a progestagen as well as estradiol
  – Supplementation with which steroid actually prevents abortion?
Questions?