HORMONE THERAPY IN EQUINE REPRODUCTION

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HORMONE THERAPY IN EQUINE REPRODUCTION

- GnRH agonists
- Gonadotropins
- Gonadal Steroids
- Miscellaneous
  - Prostaglandins
  - Oxytocin
  - Domperidone
- Alternative therapies

HUMAN CHORIONIC GONADOTROPIN

- Large glycoprotein hormone
- Produced by cytotrophoblast cells of the human placenta
- hCG has LH-like biological activity
- Used to induce a timed ovulation in mares in estrus
**hCG: CLINICAL USE**

- Expectation: 85 – 95% of mares will ovulate within 48 hours after hCG administration
- Average interval to ovulation is approximately 36 hrs

**hCG: REPEATED USE**

- Repeated administration of hCG results in development of anti-hCG antibodies
- Repeated administration of hCG during one breeding season may lead to a decrease in efficacy at inducing a timed ovulation
- Adverse effects (if any) are presumed to be due to the presence of these antibodies

**DESLORELIN**

- Small peptide hormone (9 amino acids)
- Potent agonist of GnRH
- Non-immunogenic
- Efficacy remains after multiple uses during same breeding season
- SucroMate™ is approved by USA-FDA
DESLORELIN

- ~ 90% of mares ovulate within 48 hours after administration
- No decrease in efficacy with repeated use reported
- No adverse effects reported

DESLORELIN INJECTION

Comparison: Deslorelin vs hCG

<table>
<thead>
<tr>
<th>Group</th>
<th>(n)</th>
<th>Follicle (mm)</th>
<th>Edema Score</th>
<th>Interval to Ov. (days)</th>
<th>% Ov. within 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>19</td>
<td>38.9 ± 2.2</td>
<td>1.3 ± 0.8</td>
<td>3.1 ± 1.6</td>
<td>36.8 % a</td>
</tr>
<tr>
<td>hCG</td>
<td>128</td>
<td>40.3 ± 2.9</td>
<td>1.6 ± 0.7</td>
<td>2.0 ± 0.7</td>
<td>88.3 % b</td>
</tr>
<tr>
<td>Deslorelin</td>
<td>121</td>
<td>40.4 ± 2.8</td>
<td>1.6 ± 0.8</td>
<td>1.9 ± 0.7</td>
<td>90.1 % b</td>
</tr>
</tbody>
</table>

Comparison: Deslorelin vs hCG

Equine Follicle Stimulating Hormone (eFSH)

- Commercially available in U.S. from Bioniche Animal Health USA, Inc
- Beginning in 2003
- Not available in 2008 or 2009 (?)
- Highly purified FSH preparation derived from equine pituitaries
HORMONE THERAPY: EQUINE FSH

**Indications:**
- Superovulation in cycling mares
- Stimulation of follicular development in transitional or acyclic mares

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Equine Follicle Stimulating Hormone (eFSH)

**Protocol:**
- Begin eFSH treatment (12 mg, IM, BID) 5-7 days after ovulation when a cohort of follicles is 20-25 mm in diameter
- Administer prostaglandins one day after the onset of eFSH treatment
- Stop treatment once follicle(s) are > 30 mm in diameter
- ‘Coast’ for 36 hours
- Administer hCG if follicle(s) are > 35 mm

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eFSH: CLINICAL TRIALS

<table>
<thead>
<tr>
<th>Group</th>
<th>Ov Rate</th>
<th>Preg Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycling (US)</td>
<td>3.4 ± 0.7</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td>Cycling (Brazil)</td>
<td>3.6 ± 0.5</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>Control</td>
<td>1.0 ± 0.0</td>
<td>0.5 ± 0.1</td>
</tr>
</tbody>
</table>
**eFSH: CLINICAL TRIALS**

**Transition Period**

<table>
<thead>
<tr>
<th>Group</th>
<th>(n)</th>
<th>No. (%) Ov</th>
<th>Int to Ov</th>
</tr>
</thead>
<tbody>
<tr>
<td>eFSH</td>
<td>10</td>
<td>8 (80.0)</td>
<td>7.6 days</td>
</tr>
<tr>
<td>Controls</td>
<td>10</td>
<td>0 (0.0)</td>
<td>34.9 days</td>
</tr>
</tbody>
</table>

Dose of eFSH = 12 mg, IM, BID

hCG administered once follicle(s) > 35 mm

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**ALTRENOGEST**

- Synthetic progesterone
- Regumate® approved for use in the mare for suppression of estrus
- Regumate® now off patent in USA
  - Several other altrenogest products now available
    - Paste
    - Injectable

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**Regumate®**

**Common Clinical Uses:**

- Management of the transition period
- Suppression of estrous behavior
- Estrous synchronization
- Maintenance of pregnancy / luteal insufficiency
  - Dose is 1 ml per 50 kg/110 lbs (approx. 10 mls)
  - Up to 120 days of pregnancy (or as needed)
- High-risk pregnancy (20 mls)
LONG-ACTING PROGESTERONE

Example:
BioRelease P4 LA

Indication:
- Maintenance of pregnancy
- Compounded by BET Pharm (Lexington, KY)

Dosage:
- 10 ml dose contains 1500 mg of P₄
- P₄ concentration decreases to less than 4 ng/ml by 8-10 days after administration

Clinical Trial:
- Compared maintenance of pregnancy for BET-LA-10D (every 7 days) vs Regumate® (daily) in a prostaglandin challenge model
- Pregnant mares were treated beginning on day 18 and administered PGF on day 18
- Pregnancy monitored by ultrasound out to day 45

LONG-ACTING PROGESTERONE

Clinical Trial:

<table>
<thead>
<tr>
<th>Group</th>
<th>(N)</th>
<th>No. (%) Preg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (no PGF)</td>
<td>7</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td>Estrumate</td>
<td>7</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Regumate</td>
<td>7</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td>BET-LA-10D</td>
<td>7</td>
<td>7 (100)</td>
</tr>
</tbody>
</table>


PROGESTERONE IMPLANTS: SYNOVEX®

Synovex® Implants:
- Used to promote weight gain and feed efficiency in cattle
- 8 Synovex® pellets contain 200 mg progesterone and 20 mg estradiol benzoate

SYNOVEX®

Synovex® Implants:
- Release period: 100-150 days
- Potentially, 1.3 to 2.0 mg progesterone per day is released from the implant
- 100-150 mg progesterone per day required to suppress estrus
- 200 mg progesterone per day required to maintain pregnancy
Synovex® Implants:
- In a controlled clinical trial, administration of 8, 32 or 64 pellets did not suppress estrus in mares
- Administration of 8 pellets resulted in undetectable blood progesterone levels in geldings
- Use in performance mares for estrus suppression is not supported or recommended
- Not approved for use in the horse

McCue et al., J Eq Vet Sci 1997;17: 327-329

SYNTHETIC PROGESTINS

The inability of some synthetic progestagens to maintain pregnancy in the mare


SYNTHETIC PROGESTINS

Clinical Trial:
- Compared maintenance of pregnancy for several synthetic progestins in a prostaglandin challenge model
- Pregnant mares were treated beginning on day 16 and administered PGF on day 18
- Pregnancy monitored by ultrasound

SYNTHETIC PROGESTINS

Progestins:
• Altrenogest (Regu-Mate®)
• Medroxyprogesterone (Depo-Provera®)
• Hydroxyprogesterone (Hyproval®)
• Norgestamet (Norplant®)
• Megesterol acetate (MGA®)


Results:

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>No. mares</th>
<th>Treatment</th>
<th>Week(s) after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6</td>
<td>1000 mg medroxyprogesterone acetate; 7 days (4 IM)</td>
<td>4.4 ± 0.8</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>500 mg medroxyprogesterone acetate; 4 days (1 IM)</td>
<td>3.8 ± 1.7</td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>500 mg medroxyprogesterone acetate; 4 days (1 IM)</td>
<td>3.6 ± 1.9</td>
</tr>
<tr>
<td>D</td>
<td>6</td>
<td>500 mg medroxyprogesterone acetate; 4 days (1 IM)</td>
<td>3.6 ± 1.5</td>
</tr>
</tbody>
</table>


EFFICACY OF MEDROXYPROGESTERONE FOR ESTRUS SUPPRESSION IN MARES

CSU (2007)
• Clinical trial to compare medroxyprogesterone and altrenogest for suppression of estrus
• 18 normal* mares (n=6 per group)
  ◦ Control - saline placebo IM once per week for 6 weeks
  ◦ Altrenogest - 10 mls orally once daily for 6 weeks
  ◦ Medroxyprogesterone acetate
    • 1600 mg initial (loading) dose IM
    • 400 mg once per week IM for 6 weeks
**Teasing behavior**

Yellow = estrus  Green = diestrus

**LH Concentrations**

Blue = Saline  Pink = MPA  Green = Altrenogest

**RESEARCH CONCLUSIONS**

Medroxyprogesterone acetate (Depo-Provera®)

- A loading dose of 1600 mg followed by weekly doses of 400 mg did not:
  - Suppress behavioral estrus
  - Inhibit follicular development or prevent ovulation
  - Alter pituitary LH secretion
- Use of MPA for estrus suppression cannot be supported
**PROSTAGLANDINS**

Two types commercially available in USA:

- Estrumate® (cloprostenol)
  - Dose 250 µg, im (1 ml)
- Lutalyse® (PGF2α)
  - Dose 10 mg, im (2 mls)

**Indications:**

- Luteolysis: Effective 5-15 days after ovulation
- Synchronization of estrus
- Terminate unwanted pregnancies
  - Multiple doses may be required after day 35
- Evacuation of uterine fluid
  - Induces uterine contractions for 2 - 4 hrs

**EVACUATION OF UTERINE FLUID**

- Potential for adverse effects on CL formation when used in the post-ovulation period
PROSTAGLANDIN THERAPY

- PGF administration prior to ovulation has no effect on $P_4$ levels
- PGF administration after ovulation is associated with significantly lower $P_4$ levels (may recover in some horses)
- Oxytocin treatment after ovulation does not effect $P_4$ levels

Effect of cloprostenol in the periovulatory period on CL function

PROSTAGLANDIN THERAPY

- Pregnancy rates are lower in mares administered prostaglandins in the early postovulation period

Brendemuehl AAEP Proceedings 2001: pp 239-241
**Evacuation of Uterine Fluid:**
- PGF or Oxytocin *prior to* ovulation
- Oxytocin (only) *after* ovulation

**Clinical Uses:**
- Evacuation of uterine fluid
- Induction of labor
- Management of retained placenta

**Common Dosage:**
- 5-20 units, iv or im
- No long-acting oxytocin in USA

**DOPAMINE ANTAGONISTS**

**Indication:**
- Management of fescue toxicity
- Stimulation of lactation
- Induction of follicular development in transitional mares
**DOMPERIDONE**

**Common Dosage:**
- 500 mg orally once daily

**Efficacy:**
- Effective at inducing lactation
  - Treatment of post-partum mare with agalactia
  - Induction of lactation for a nurse mare
- Ability to stimulate follicular development is controversial

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**PROSTAGLANDIN E₁**

**Indication:**
- Topical application of PGE₁ (Misoprostol; Cytotec®, Pfizer, Inc) has been used in attempts to promote cervical relaxation in mares (i.e. older maiden mares)
- Efficacy controversial
- Compounded cervical cream

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**HORMONE MODULATION: INTRAUTERINE GLASS BALLS**

**Indication:**
- Suppression of estrus in cycling mares

*Nie et al., 2001*
HORMONE MODULATION: INTRAUTERINE GLASS BALLS

- Sterilized glass ball (35 mm marble) inserted into the uterus during estrus
- 5 of 12 (42%) remained out of heat for an average of 3 months
- Estrus suppression due to formation of persistent corpora lutea

Nie et al., 2001

HORMONE MODULATION: INTRAUTERINE GLASS BALLS

- Uterine prostaglandin secretion pattern altered
- Removal resulted in eventual return to estrus
- No significant uterine problems noted due to treatment

Nie et al., 2001

GnRH VACCINE

- Administration of a vaccine against gonadotropin releasing hormone (GnRH) has been used to block estrus and as a contraceptive agent
- Approved for use in horses in Australia (Equity™; Pfizer Animal Health)
A recent clinical trial was conducted in Canada. Vaccination resulted in temporary suppression of estrus and blocked fertility (one season). Mares resumed cycling and a majority became pregnant the following year.

Anecdotal reports from Australia indicate that some mares vaccinated as yearlings or 2-year-olds did not cycle for several years afterward. The Equity™ vaccine has recently been withdrawn from the market in Australia.

A limited clinical trial at Colorado State University suggest that the Canine GnRH vaccine (Pfizer), marketed for treatment of benign prostatic hyperplasia may also have efficacy in suppression of follicular development in the mare.

(McCue, 2009 unpublished data)