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POTENTIAL TREATMENTS FOR REPRODUCTIVE PROBLEMS IN ELEPHANTS

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GnRH (for ovarian cysts)
A common treatment for ovarian follicular cysts in dairy cattle is GnRH (e.g., Cystorelin@, The Butler Company, 12235 S. Laramie Ave, Alsip IL 60658; 1-800-551-3861). We recommend a dosage of 1,000 µg, i.v. (i.e., 10 times the cow dose). Similar doses have been used in other elephants with no harmful side effects. Because elephants exhibit two LH surges during the normal follicular phase with the second one inducing ovulation, we are looking at two potential treatment options: 1) a single injection and daily blood sampling for 4 weeks to determine if a second, spontaneous LH surge occurs; or 2) two GnRH injections, given 3 weeks apart to induce two surges. To assess pituitary responses, we recommend frequent blood samples be collected on the day of GnRH injection. A recommended blood sample schedule is as follows: -30, -15, 0 min (followed immediately by GnRH injection); 15, 30, 45, 60, 75, 90, 120, 180, 240 min post-GnRH. For option #2, we recommend collecting daily blood samples for 30 days after the first GnRH injection to determine if a second, spontaneous LH surge will occur.

Regumate + GnRH (for acyclicity or irregular cycles)
Oral progestins, like altrenogest (Regumate®, Intervet Inc., Millbsboro, DE), are effective treatments for anovulation in some species. We recommend administering Regumate orally (160 mg per day) once a day for 30 days. This should suppress follicular development until removal of the progesterone block. In normal cycling cows, the first LH peak occurs 2-4 weeks after the progesterone drop. Regumate treatment might induce a normal LH surge after treatment withdrawal. But in case it does not, we recommend stimulating an LH surge with GnRH (1,000 µg, i.v.; Cystorelin, Factrel or equivalent) 3 weeks after the withdrawal of Regumate. To assess treatment responses, we recommend blood samples be collected twice weekly during Regumate administration until the GnRH injection. If possible, frequent samples should be collected on the day of GnRH injection to assess the pituitary response to GnRH. A recommended blood sample schedule for the GnRH challenge is as follows: -30, -15, 0 min (followed immediately by GnRH injection); 15, 30, 45, 60, 75, 90, 120, 180, 240 min post-GnRH. We further recommend collecting daily blood samples for 30 days after the GnRH challenge to determine if a second, spontaneous LH surge and ovulation will occur.

Equidone (domperidone)
Equitox Pharma contacted us about their product, EQUIDONE® oral gel (domperidone), which is used to treat reproductive problems in mares. Information on this drug is available at their website www.equitox.com under the research tab. There also is a published paper on the effect of

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domperidone on follicular development in mares (J. Reprod. Fertil., Suppl. 56:185, 2000). Domperidone is a dopamine antagonist that stimulates prolactin secretion from the pituitary after oral administration. It has been shown to have a wide margin of safety in numerous species. Doses for elephant reproductive problems have been based on metabolic scaling of treatment regimens for pregnant and nonpregnant mares. The drug will be provided free of charge by the company. There are three possible uses of this drug that could benefit elephants:

1. *Potential treatment of 'flatliners'*
   - Mares treated with domperidone during seasonal anestrous developed follicles that appeared functionally normal. In other species, prolactin increases during the follicular phase and may be necessary for normal follicular development. We also have data showing that prolactin is significantly elevated during the follicular phase in African elephants. Thus, it is possible that prolactin is needed for stimulating follicle development and ovulation in elephants.
   - The treatment regimen for acyclic or irregular cycling elephants is intended to mimic the cyclic changes in prolactin that occur during the normal estrous cycle in the female African elephant. It will consist of a cyclic regimen of daily administration (2 grams/d) for 8 weeks followed by no treatment for 4 weeks, then 8 weeks of treatment, etc. until efficacy can be determined. Treatment can be initiated at any time in acyclic females. For irregular cycling cows, treatment should start 1 week after the end of the luteal phase (i.e., after the drop in progesterone). Blood samples should be collected weekly during the treatment period for progestin and prolactin analyses.

2. *Prevention of dystocia'*
   - The drug has been used in mares to ensure easier parturition and to avoid problems associated with difficult births. The increase in prolactin stimulated by Equidone facilitates relaxation of the gluteal muscles, stimulation of mammary gland development, softening of the cervix, enlarging of the vulva, and enhancement of 'broodiness'. We know that prolactin immunoactivity increases after the 7th month of gestation in both Asian and African elephants. Additional prolactin stimulated by Equidone might be of some use as a preventive measure against birthing difficulties and/or to improve maternal care immediately post-birth. Treatment (2.5 grams/d) should begin 30 days before expected parturition and continued daily until birth. Blood samples should be collected 2-3 times per week during treatment for progestin and prolactin analyses.

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3. *Treatment of agalactia or poor milk production*
   - Increased prolactin induced by Equidone can stimulate milk production, and in horses has been shown to stimulate milk production even in barren mares. Thus, for elephants that experience difficulty in nursing a calf immediately after parturition, Equidone could ensure lactation continues until the cow-calf bond is formed and calf is able to nurse on its own. It might also increase the chances of calf acceptance due to prolactin's stimulatory effect on mothering ability. Treatment (500 mg/d) should begin immediately after parturition and continued daily until the calf nurses normally (suckling will take over stimulation of continued lactation). Blood samples should be collected 2-3 times per week during the treatment period for prolactin analyses.

Beta-Carotene Supplementation (for acyclicity or irregular cycles)

Follicular growth and development, ovulation and pregnancy maintenance require adequate levels of Vitamin A (e.g., ß-carotene). Conversely, insufficient ß-carotene can cause delayed ovulation, luteal insufficiency and increased incidence of ovarian follicular cysts. Feeding ß-carotene (300-500 mg/day; ROVIMIX®, Roche Vitamins, Ltd.) has been effective in treating fertility problems in dairy cattle. A similar treatment might be effective in treating acyclicity or irregular cyclicity in elephants. Elephants should be dosed at ~6 times the cow dose (i.e., ~2300 mg/day). Plasma ß-carotene levels should be checked to determine appropriate supplementation dosage. The nutrition laboratory at Michigan State University (517-353-1683) will do beta carotene analyses. Animals can be treated indefinitely.

Vitamin/Mineral Supplements (for acyclicity or irregular cycles)

1. *Super Gain from Horse Guard (http://www.horseguard.biz)*
   - Product literature claims this to be the "most potent complete supplement available" for horses. It further states, "Vitamins are in the most stable and available forms. Minerals are a balanced combination of inorganic and proteinate (chelated) forms. This combination offers the highest availability and benefit to the animal. XP Yeast aids digestion for improved food utilization. Palatable corn and wheat form the base of **Horse Guard's** convenient-to-feed pellets."
   - This product was given to a noncycling African elephant that also had a low hematocrit. Within a few months, hematocrit levels returned to normal and the female is now cycling.
   - Estimated Super Gain dose is 7 scoops per day (4 oz per scoop, 28 oz per day). To track cyclicity status, blood samples should be collected weekly for progestin analysis. Animals can be treated indefinitely.

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2. *Vita-Key Equine Supplement or Antioxidant Supplement (http://www.vita-key.com)*
    - Website claims that the Equine Supplement contains chelated minerals to enhance gut absorption, and contains high levels of all B- and fat-soluble vitamins, as well as vitamin C to ensure good nutrition. Claims for the Antioxidant Concentrate are that it provides the B-complex, C and fat-soluble vitamins, as well as all the important minerals: selenium, copper, zinc and manganese and the essential amino acids methionine and lysine. These additions are important for horses under stress or for those with arthritis problems.
    - This product has not been tested in elephants yet.
    - Estimated Supplement dose is 28 oz per day. To track cyclicity status, blood samples should be collected weekly for progestin analysis. Animals can be treated indefinitely.

An ingredient comparison between Vita-Key and Super Gain supplements is available through Vit-Key's website (http://www.vita-key.com/horse_guard_super_gain.htm).

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