Planning and management of mares and recipients for healthy pregnancies and foals

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Developmental origins of health and disease

The developmental origins of health and disease (DOHaD) in horses is a growing area of investigation that concerns the way the maternal environment influences the foal's future health. Maternal environmental clues program important physiologic adaptations in the foal such as: conformation, energy homeostasis, osteochondral health, and thyroid function.[1]

This topic was also investigated and described as 'fetal programming' where placental, fetal and postnatal development were studied.[2,3] Maternal nutrition during pregnancy, stress and exposure to harmful substances during critical time periods are known to have an effect on the overall health of her offspring.[1-3] The foundational research on the DOHaD involves studies on epigenetic mechanisms.

Epigenetic mechanisms

'Epigenetic' is a term applied to the myriad complex interactions between the genome and environmental factors during development and differentiation. Epigenetic mechanisms are induced by modifications of the cellular environment. Epigenetic mechanisms include DNA methylation and posttranscriptional modification.[4] The methylation of DNA can block binding of transcription factors, this is a mechanism where expression of unwanted or surplus genes may be suppressed. Methylation of DNA is referred to as an 'epigenetic mark'. As a cell divides these epigenetic marks are propagated, which becomes a non-genetic means of altering physiologic functions. The epigenetic marks may result in physiologic effects a very long time after the event that resulted in their formation, occurred.[1] For example, in pregnant rats a low protein diet has deleterious effects on the health of her offspring, where the rat mother's low protein diet results in the birth of pups with altered mRNA expression attributed to epigenetic processes.[5]

Periconceptional period

What has recently been described is how the periods just before and just after fertilization, in what is called the pre and periconceptional period, are important in the DOHaD.[1,4] The periconceptional period spans the time from fertilization to blastocyst development. Patterns of gene expression in the embryo are modulated by events such as DNA methylation and histone modification, in a process termed 'epigenetic regulation'.

The dynamics of the methylation pattern is also affected by processes during development, and are influenced by maternal age, parity and gender. 'Deep epigenetic modifications' occur during the development of the gametes.[1,4] The mother's and father's nutritional status at the time of gamete formation is therefore important. Research has shown that gamete development is influenced by the nutritional status of the dam and sire during their production, after fertilization and during the periconceptual period.[4] Assisted reproductive procedures may impact health and alter subsequent metabolism, cardiovascular function and body weight of the individual.[1,6] The milieu during pregnancy and neonatal life, has been reported to have long-term effects. There is however some plasticity in individuals, because epigenetic modification occurs throughout the life of the individual.[1]

In females, oocytes are formed in fetal life and then decrease over the life of the individual, in males, testicular germinal epithelial cells begin active division at puberty and constantly produce sperm through the process of spermatogenesis. Therefore, epigenetic process that involved gametes may produce different effects due to the functional and structural differences in male and female gametes.

Effect on assisted reproductive technologies

The conditions for successful embryo technologies include optimized culture media for gametes and embryos.[5] Problems with *in vitro* fertilized embryos, such as large offspring syndrome, are believed to be a result of epigenetic processes.[4,5,7] *In vivo* and *in vitro* derived equine embryos show different patterns of gene expression.[6] The difficulties with somatic cell clone nuclear transfer are also attributed to altered gene regulation by epigenetic processes during embryonic genome activation, which leads to developmental defects in embryos.[7]

In utero development

Many factors that influence a mare's health also play a role in the health of the mare's foals. The health of the brood mare in terms of her metabolism, nutrition, and whether assisted reproductive technologies, such as embryo transfer or intracytoplasmic sperm injection, were utilized to establish the pregnancy, have been shown to affect: feto-placental development, foal birth weight, and foal growth.[8] The effects of breed using cross over studies of larger and small breed embryo donors and embryo recipients has been described in horses.[1,8] Walton and Hammond (1938) using artificial insemination crossed Shetland pony mares and Shire draft horses to illustrate these differences, and they showed that the mare carrying the pregnancy regulated fetal size, and post-natal growth rate of the foal.[1,8] As expected of these crosses the Shire offspring of Shetland pony mares remained smaller as adults and Shetland offspring of Shire mares remained larger as adults.[8] Other researchers studied osteochondral health of foals born following a pregnancy that involved embryo transfer and a size mismatch. This research illustrated why matching donor and recipient mare size is advantageous in reducing osteochondrosis in foals.[9]

Nutrition and feeding practices

In the feral state mares would typically foal in spring near the time of lush pasture availability, and then encounter less abundant feed in autumn and even less in winter. The feral mare supports the final growth of the foal often using her energy reserves.[1] Foaling would coincide around the time the resurgent growth of pasture occurs. The National Research Council (NRC) however recommends feeding mares a maintenance diet through the fifth month of pregnancy and then increasing the mare's plane of nutrition to account for fetal growth.[10] While this feeding recommendation makes sense to prevent weight loss during pregnancy, there is a mismatch between the natural ebb and flow of energy that a feral horse would encounter and the subsequent body weight changes a feral mare would experience induced by those energy flows, and the currently recommended NRC feeding practices. How our feeding practices influences epigenetic events in horses is currently an area requiring further investigation.

Half of the cost of keeping horses is feeding them.[11] An evidence-based feeding program is best to optimize horse health. Some very interesting epidemiologic studies showed that mares fed concentrate during pregnancy had foals of similar birth weight compared to mares that were fed only forage. The foals of Belgian Ardennes mares fed the concentrate however had a prevalence of osteochrondrosis of 33-38% while those mares fed forage had an eight-fold reduction in OCD in their foals compared to the grain fed mares, that is a 4% prevalence of OCD.[12] The foals born to the grain-fed mares, however had better regulation of glucose, but delayed puberty, and thinner cannon bones. The effects of grain feeding the mare on the foal's subsequent glucose homeostasis, likely occurs through epigenetic mechanisms and the subsequent changes in the processes and hormones that regulate metabolism and maturation.[1,12]

The pregnant mare is often overfed during pregnancy (eating for two) and underfed during lactation. The reality is that many mares enter the breeding season already overweight. A report on body condition of horses in Saskatoon, Saskatchewan, Canada revealed that 20% of horses are over-conditioned and 8% are obese.[13] It is common for many brood mares to have a BCS of 7/9. In Europe it is estimated that mares in late pregnancy are fed from 10-40% more than their nutritional needs.[1] Practitioners should encourage mare owners not to normalize excess body condition in mares. The trends in body condition scores or mare weights should be recorded as part of herd management. Mares should enter into pregnancy with a healthy body condition. Ideally mares should have a BCS of 6/9 during pregnancy.

Adult horses with free access to pasture may spend up to 90% of their 24-hour time budget eating. Mares with free access to forage may consume 3% of their body weight in kilograms when they only require 1.5-2%, for maintenance and early-mid pregnancy.[10,11] Mare's access to pasture may need to be limited, as pasture provides 24-7 availability of feed, and unlike the feral horse a subsequent decrease in feed availability is not encountered. Pasture grasses are high in vitamins and beta carotene, they are also full of highly digestible carbohydrates.[15] Lush grass may be problem for horses with heavier body condition, and for mares that have endocrine or metabolic problems. These endocrine (for examine pituitary pars intermedia dysfunction; PPID) and equine metabolic syndrome mares are predisposed to develop laminitis. Laminitis in horses is now reported to be a syndrome, rather than just an acute event, and it is reported that endocrine factors are involved in many horses.[14]

Supplementation of most mares with concentrate or richer forage such as alfalfa, does not need to occur before the last third of pregnancy. It is common although unwise, for mare owners not to have a feed analysis performed on their hay. An analysis of the hay assists with the choice of a ration balancer and or mineral mixture. As the mare nears foaling the fetus will gain about 0.5 kg/day. The mare's nutritional needs increase so she needs 20% more digestible energy to maintain body weight. This may often be accomplished by feeding more hay or a higher quality hay. Hay nets with small diamonds provide a more controlled access to the feed in a manner that more closely mimics natural grazing.[10,11]

Vitamins and minerals

The relationship between micronutrients and health was recognized in North America in the 1930's when iodine deficiency and thyroid disease, which characteristically resulted in goiter formation, was identified in both people and horses. Iodine deficiency was linked to the low iodine content of the soil and diet, which resulted in goiter formation, and hypothyroidism.[11,15] Other micronutrient deficiencies, such as selenium, were identified and associated with white muscle disease in horses.[16] Copper deficiency in horses was associated with poor hair coat, anemia and orthopedic disease. Zinc deficiency was associated with poor hair coat, lower fertility and impaired immune function, copper deficiency results in poor hair coats, anemia and orthopedic disease.[10,11]

Micronutrients are an essential part of any feeding program. Micronutrients include trace minerals important for horses such as the aforementioned: iodine, copper, selenium, and zinc but also includes some vitamins such as A and D.[10,11] These nutrients are key to equine health as they are required for: metabolic function, growth, milk production, and reproduction. Requirements for vitamins and minerals are higher during pregnancy.

An ongoing concern is that because horse owners do not routinely analyze their forages, they guess at the level of mineral supplementation required for their mares, and may use only mineral blocks for supplementation. This commonly results in horses having an inadequate nutritional intake of micronutrients, such as iodine, selenium, zinc and copper in their diet.[10,11] In addition, consumption of minerals by horses is uneven, when minerals are provided *ad libitum* in salt-based blocks, or as a loose mixture. Most horses do not consume enough of the block minerals to meet their requirements.

In spite of changes in climate and agricultural practices there has been little monitoring of changes in the important micronutrients in the equine population. A 2014 study by the Saskatchewan Forage Council of trace minerals in pastures showed that native and cultivated pasture grasses had insufficient copper and zinc levels to meet the needs of beef cattle.[15] As horses graze these same areas, similar results should be expected. Other trace minerals were shown to vary by plant species, season and soil zone, indicating that mineral supplementation programs should be based on measuring actual values. Selenium deficiency may result in lower glutathione peroxidase and vitamin E levels.[17] Waldner and coworkers in reported in a comprehensive series of studies of beef cattle herds in western Canada that: forages were often deficient in zinc and copper, 43% of cows were copper deficient, vitamin E deficiencies were present in abortuses/stillbirths, and selenium deficiency was present in some neonatal calves.[18] Forages for horses are grown in the same regions and soils as cattle, and contain the same plant species, hence it is likely that they have similar nutritional characteristics, including micronutrient deficiencies.

Authors report micronutrients may be monitored through laboratory analysis of mane hair or serum analysis[19,20] Micronutrient levels have been reported in mare and foal serum and mane hair.[19,20] Feeding practices have been reported to affect mineral levels in mane hair.[20] Fetal foal hair forms from about seven months of pregnancy to term, hence the trace minerals in foal mane hair at birth represent a snapshot of the foal's *in utero* exposure. The analysis of the trace minerals in a foal's mane hair may be a useful tool to analyze the nutrition program of the dam. A periodic analysis of mare serum and newborn foal hair for trace mineral levels would provide valuable information on the feeding program of the farm.

The thyroid health of the mother has been identified as a key determinant of her foal's future health and disease. Dietary factors such as iodine deficiency or excess in mares, are known to cause congenital goiter in foals. Changes in thyroid hormone levels are related to iodine in the diet in cases of deficiency and excess. Exposure of pregnant mares to excess nitrate, plants that disrupt iodine utilization, and trace mineral deficiencies have been found to be risk factors for a disease of foals called congenital hypothyroidism dysmaturity syndrome (CHDS). The consequences of CHDS are dramatic and include: thyroid hyperplasia, limb contracture/tendon ruptures, mandibular prognathism, umbilical problems, and severe carpal and tarsal boney dysgenesis. Due to abnormal musculoskeletal development, CHDS foals are either euthanized, or experience high rates of developmental orthopedic disease.[21,22] Horses may be exposed to goitrogenic plants and seeds (*Brassica* family) due to cultivation and spread of oilseed plants (mustard, canola) and through consumption of pasture weeds. Goitrogenic plants contain glucosinolates that when hydrolyzed, are converted into compounds that are either thyrotoxic or that interfere with the uptake or organification of iodine.[23] Even if iodine intake is adequate these plants may result in iodine depletion over time. The dams of hypothyroid foals also have impaired thyroid function.[22] Other plants such as fescue grass infected with the fungal endophyte, *Neotyphodium coenophialum,* also pose a risk to pregnant mares. Ingestion of endophyte infected fescue may lead to a series of clinical problems such as: prolonged gestation, dystocia, agalactia (ergopeptides mimic dopamine and act to suppress prolactin secretion), failure of passive transfer, and suppressed fetal thyroid function. Mares need to be off fescue pasture for a month before foaling, and/or administered domperidone orally daily for 10 days prior to parturition to help prevent premature separation of the placenta (red bag delivery) and agalactia.[24,25]

Nutrition summary

Appropriate feeding of pregnant mares and stallions is important for the long term health of the foal. Epigenetic processes begin during gametogenesis of the parents and continue in the periconceptual period. Fetal development and postnatal growth of the foal is affected by the conditions of pregnancy, such as uterine size, and feeding of the dam. Recipients of embryos should be similar in size and breed to the donor mares. Minimal grain feeding to pregnant mares should be considered to prevent metabolic alterations that may lead to osteochondrosis in her foal. Mineral salt block access alone is unlikely to supply sufficient trace minerals for the requirements of pregnancy. Plants such *Brassica* family mustard plants and endophyte infected fescue may result in disease and suppress thyroid function. Serum or milk trace mineral analysis is a direct way to detect mineral depletion, while function markers such as thyroxine, vitamin E, or glutathione peroxidase are more helpful in identifying diseases caused by an underlying deficiency, or glandular dysfunction.[23]

Embryo transfer recipient selection

The recent research points to the need for excellent multi-generational management of horses. Embryo transfer recipient mares should preferably be similar in size and breed to donor mares to minimize epigenetic problems. Mares under the age of 12 are generally preferred, as this corresponds to the most fertile years of a mare's life. Preferably recipient mares are tractable and have had a successful foaling. The recipients should have no history of reproductive problems, and they should be in good body condition at breeding. They should have normal estrous cycles. Excellent perineal conformation is desirable.[26]

Synchronization of recipients

Hormonal treatment may be utilized with anestrus, transitional and cycling, recipient mares to simulate the conditions of a mare that has been in estrus, or align the donor and recipient mare's ovulation. The ovulation of donor and recipient mares should be closely aligned. Generally, it is desirable for the recipient mare to ovulate from one day before the donor's ovulation and up to three days after the donor's ovulation.[26]

Seasonal asynchrony between donors and recipients

If the donor mare is cycling because she was treated with artificial light, and the available recipient mares are in deep anestrus or transition, anestrus and transitional mares may be treated to prepare them for an embryo transfer. The protocol for the prospective recipient is started on the day the donor ovulates. The recipient is administered 6.6 mg estradiol 17β IM for two consecutive days followed by 5 to 7 days of a short-acting progesterone preparation (200 mg, IM, q 24h). She is then ready for a transfer. Supplemental progesterone must then be provided using daily administration of altrenogest (0.44 mg/kg) or treatment using long-acting progesterone formulations (1,500 mg, progesterone IM), or long acting altrenogest (150 mg) IM once weekly, and continued if the pregnancy has been established for 100 days.[27] There is a microparticle compounded formulation of altrenogest that has activity for 30 days. An alternative protocol involves on the day of the donor ovulation beginning recipient treatment with estradiol benzoate for 3 days once daily IM using 5mg, then 3 mg, and followed by 2mg of estradiol benzoate and 400 mg of long-acting progesterone weekly until 120 days.[27]

Cycling but asynchronous donors and recipients

There are newer hormonal strategies to try for aligning donor mares and recipients. Recipient mares in early diestrus (days 1-5) may be administered two doses of prostaglandin F2alpha (PGF) 24 hours apart as the early corpus luteum is more resistant to prostaglandin, and mares from day 5-16 may be administered one 5 mg SQ dose of PGF. The follicular structures on the ovary at the time of PGF treatment in cycling mares determines the time to estrus. Follicles typically grow at 3 mm per day. Mares typically start to exhibit signs of estrus when a dominant follicle reaches 30 mm. The timing of the PGF treatment therefore needs to include consideration for the follicle size of the donor and recipient to align their estrus. Ovulation induction agents are then utilized to further tighten the synchrony.[26]

To align diestrus mares with estrus donor mares, diestrus recipient mares may be administered PGF and 10 mg estradiol-17β IM on the day of or the day after the donor mare's ovulation (Day -4). The administration of estradiol-17β was repeated on Day -3 (10 mg estradiol-17β IM), Day -2 (20 mg estradiol-17β IM), and Day -1 (10 mg estradiol-17β IM). On Day 0 (named to mimic the ovulation day), mares received long-acting altrenogest (300 mg IM). Recipient mares treated in this fashion, appear to be able to receive embryos from Day +3 to Day +8 after long-acting altrenogest (300 mg IM). Prior to the transfer of the embryo the recipient mare received a second treatment with altrenogest and had uterine features assessed. In these recipient mares on days +10 to +12 a second treatment with long acting progesterone (1500 mg) was administered.[28] If the transferred embryo is present in the recipient mare, then long acting progesterone is administered once a week until 100 days or until supplementary corpora lutea form. Altrenogest has also been administered.[28]

Management of pregnant mares

Mare group size

It is strongly recommended to keep pregnant mare groups stable, with small groups sized (fewer than 20 mares), with mares of similar ages, after the fifth month of pregnancy.[29] Pregnant mares should not have fenceline contact with horses that come and go from the farm, or new arrivals. Large groups of mares in enclosed areas may create stress as horses have a strong social hierarchy. Horses when confined constantly vie for preferred access to food, water, and shelter and have a social ordering that controls access.[28] In feral conditions, bands of horses are often small and are comprised of around three mares and a stallion. Disruption in the social order may results in the shedding of equine herpesvirus 1. Mares become susceptible to EHV-1 abortion after the fifth month of pregnancy.[30]

Dental care

Mares with poor body conditions should have a thorough dental examination performed and their teeth floated if needed. Generally, it is preferabe to perform the necessary dental work under sedation. If heavy sedation is required and there is concern expressed by the owner regarding the stimulatory actions of the alpha agonists on the myometrium, the alpha agonist sedatives may be reversed.[31]

Vaccination

The veterinarian plays a major advisory role concerning vaccination along with local disease pressures, the risk of exposure, the risk and consequences of the disease, vaccine effectiveness, potential for vaccine related adverse events and cost of the vaccine. Biosecurity and biosecurity practices of the facility should be considered. Recommended information about vaccines includes: vaccines are 100% effective in preventing disease, pathogen strains may change over time, horse age and vaccine history influences response, booster vaccinations are generally required for good immunity, and vaccinations are complementary to good management. A good starting point is the information on core and risk-based vaccines for mares (Table) published by the American Association of Equine Practitioners.[30]

Equine Herpesvirus (EHV-1) abortion is the cause of viral abortion pregnancy. Key points to remember is that colostral antibodies do not prevent infection with EHV-1 in foals, horses are infected with EHV-1 as foals, and a high percentage of infected horses develop latency. No EHV-1 vaccine that can eliminate the EHV-1 carrier state. The available vaccines do not protect against infection, reinfection, or coinfection with similar strains of EHV-1, hence the goal with vaccination is to modulate the immune response to reduce shedding, viremia and clinical disease. Veterinarians often recommend vaccination of mares against EHV-1 (viral abortion) using a killed virus vaccine* at 5, 7 and 9 months of pregnancy, but there is no substitution for good management in the prevention of herpesviral (EHV-1) abortion. In addition, core vaccinations are usually administered at 4-6 weeks before a mare's due date, to increase the levels of specific antibodies present in her colostrum.[30,32]

Parasites and deworming

Tick burdens vary by location and weather factors. There are no tick products approved for use in horses. Ticks are usually manually removed. Ticks may carry certain infectious diseases (Lyme disease), *Borrelia burgdorferi,* and piroplasmosis (*Theileria equi*), and *Babesia caballi.*[30] Rather than blanket deworming, fecal egg counts are commonly performed. Low burdens are generally considered to be less than 200 eggs per gram (epg) of feces, and these horses are not treated. Higher burdens of nematodes such as strongyles should be treated using a product labeled for use in pregnant mares, such as ivermectin. Because coprophagy is a normal behavior of foals, the dam's manure is a source of parasites. Good stall, paddock and pasture hygiene decreases the risk of high worm burdens.[33]

Hoof care

It is important for mares to have their hooves trimmed on a regular basis every 6-8 weeks. This is particularly important for mares that retired from competition due to injury.[31]

Breeding management

Managed breedings allow the practitioner to precisely know the ovulation date. Mares should have an ultrasonographic examination at 15 and 25 days after ovulation to determine if twins are present. Mares that have a poor perineal conformation should have Caslick's surgery performed.

Prefoaling management

Prior to foaling a mare wellness examination is often planned. At this time the mare may be administered: a vitamin E selenium injection, booster vaccinations, and dewormed if her fecal egg count is high. A rectal and ultrasonographic examination should be performed to determine the presentation of the foal. In the majority of cases the head of the foal and orbit maybe easily identified confirming the foal is in anterior presentation. If the head cannot be identified a transabdominal ultrasonographic examination may be performed to visualize the foal's chest and the location of foal's heart within the chest. The foal's heart will be located closer to the mare's pelvis in an anterior presentation, rather than the posterior presentation where the fetal stomach is closer to the mare's pelvis than the heart. Mares with a posterior presentation are candidates for induction of parturition. The mare's vulva should be checked for the presence of Caslick's surgery and if present, the Caslick's surgery should be opened. There are increasingly convenient methods of predicting the time of parturition using calcium/magnesium or pH indicator strips. A rising prefoaling mammary secretion calcium and magnesium level and a decrease in pH from above pH of 7.0 to below 6.7 indicates impending foaling and the mare should be observed carefully for signs of foaling.[34]

*Pneumobort-K; Zoetis

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Table: Core and risk-based vaccines for use in preventive medicine programs in pregnant mares and embryo transfer recipient mares

Core Vaccines
Tetanus
Eastern Western Venezuelan Encephalitis
West Nile Virus
Rabies

Risk Based Vaccines
EHV -1
EHV-4
EVA
Influenza
Anthrax
Botulism
Strangles
Leptospirosis