Triennial Reproduction Symposium: Developmental programming of fertility

1 The importance of understanding the impacts of developmental programming on fertility: An overview. Lawrence Reynolds*, *North Dakota State University, Fargo, ND.*

Increasing evidence supports the idea that reproductive efficiency may be "programmed" during prenatal or early postnatal life. Developmental programming is the concept that an "insult" during any developmental stage can result in programming of organ/organismal function in the short or long term. Insults that result in developmental programming include external factors such as (1) malnutrition pre-mating, during pregnancy, or during infancy; and (2) exposure to environmental factors such as social stress, high temperature-humidity, smoke, herbicides, pesticides, or phytosteroids. Intrinsic factors that result in developmental programming include (1) maternal age, (2) multiple fetuses, and (3) maternal and embryonic genetic background. Based on large epidemiological studies primarily in humans, as well as controlled studies in animal models including livestock, developmental programming affects the function of various organ systems in the offspring, resulting in altered growth, body composition, metabolism, and behavior. The organ systems that have been shown to be affected include, among others, adipose tissue, brain, cardiovascular system, endocrine system, gastrointestinal tract, kidney, muscle, and reproductive system, including the ovary, utero-placenta, testis, and hypothalamic-pituitary-gonadal axis. In addition, the effects of developmental programming have been shown to be transmissible across generations. The 2015 Triennial Reproduction Symposium will focus on how developmental processes and systems can affect reproductive success in males and females in livestock and other species.

Key Words: Triennial Reproduction Symposium, developmental programming of fertility, overview

2 Beef heifer development systems and lifetime productivity. Andrew J. Roberts*[1], Rick N. Funston[2], Elaine E. Grings[3], and Mark K. Petersen[1], [1]*USDA-ARS, Fort Keogh LARRL, Miles City, MT,* [2]*University of Nebraska West Central Research and Extension Center, North Platte, NE,* [3]*Department of Animal Science, South Dakota State University, Brookings, SD.*

Research continues to amass proving nutrition and other environmental factors experienced during pregnancy affect the fetus, resulting in changes in traits exhibited through life. In livestock, small differences in nutritional profiles during gestation may result in fetal programing that alters lifetime production efficiency. Thus, the potential of fetal programing should be considered when determining supplemental feeding strategies during gestation. For example, evaluation of offspring born to cows grazing dormant pasture supplemented with either 1.1 or 1.8 kg/d of alfalfa hay during the last 3rd of gestation demonstrated females born to cows provided the lower supplementation level were 10 kg heavier and had greater BCS at 5 yr of age. These differences appeared beneficial for maintaining reproductive performance in offspring managed with less harvested feed inputs. Comparison of offspring from cows wintered on native range (low quality) or improved pasture (greater quality) for 30 to 45 d during the 5th to 6th mo of gestation resulted in a trend for longer productivity in daughters from cows wintered on improved pasture. In recent studies comparing offspring from cows with or without protein supplementation while grazing dormant winter range during late gestation, heifers from protein-supplemented dams had greater BW at weaning. This increase in BW persisted through pregnancy diagnosis and subsequent calving, and pregnancy rates were greater in heifers from protein-supplemented dams. Heifers from protein-supplemented dams appeared less feed efficient compared with heifers from un-supplemented dams. Thus, in utero exposure to nutritionally restricted environments (non-supplemented dams) may promote greater feed efficiency later in life. Nutrition during post-weaning development may also affect lifetime productivity. Heifers developed on low quality native range with RUP supplementation had greater retention beyond 3 yr of age than cohorts developed in a feed lot with higher quality feed and greater ADG. Collectively, these examples show long-term effects of nutritional management strategies used during gestation and development in given production environments need to be evaluated.

Key Words: fetal programing, lifetime productivity, nutritional supplementation

3 Effects of nutrition on reproductive development in bulls. Leonardo F. C. Brito*, *ABS Global Inc., DeForest, WI.*

A series of experiments were conducted to evaluate the effects of nutrition during calfhood (defined as the period from 10 to 26–30 wk of age) and peripubertal period (27–31 to 70–74 wk of age) on reproductive development in bulls. The overall objective of these experiments was to evaluate the effects of nutrition on endogenous metabolic hormones (leptin, insulin, GH, and IGF-I), gonadotropins and testosterone concentrations, sexual development, sperm production, and semen quality in bulls. Results of these experiments demonstrated that nutrition affected GnRH secretion and sexual development in bulls. Increased nutrition during calfhood resulted in a more sustained increase in LH pulse frequency during the early gonadotropin rise and greater testicular development at maturity. On the other hand, low nutrition during calfhood suppressed LH secretion during the early gonadotropin rise and resulted in delayed puberty and reduced testicular development at maturity. When low nutrition was accomplished by restricted feed intake, hypothalamic and pituitary function were compromised and LH secretion was more severely affected. Temporal associations between LH secretion patterns and circulating IGF-I concentrations implied that IGF-I is a possible signal to the central "metabolic sensor" involved in translating body nutritional status to the GnRH pulse generator. Nutrition also affected testicular steroidogenesis (testosterone concentrations), indicating effects on the number or function of Leydig cells, or both. Age-related increases in physiological and GnRH-stimulated circulating testosterone concentrations were hastened in bulls receiving high nutrition and delayed in bulls receiving low nutrition; these effects were probably mediated by both LH secretion and IGF-I concentrations. Circulating leptin and insulin may have only permissive roles on GnRH secretion, but may enhance testicular development. Growth hormone concentrations decreased concomitantly with increasing IGF-I concentrations during sexual development in bulls, suggesting that the testes could contribute considerable amounts of circulating IGF-I. In conclusion, management strategies to optimize reproductive function in bulls should focus on increasing nutrition during calfhood.

Key Words: bull, nutrition, sexual development

4 Nutritional programming of puberty in heifers. Gary L. Williams*[1,2], Rodolfo C. Cardoso[1,2], Bruna R. C. Alves[2], and Marcel Amstalden[2], [1]*Texas A&M AgriLife Research, Beeville, TX,* [2]*Texas A&M University, College Station, TX.*

Because multiple estrous cycles are required for heifers to express full fertility before first breeding, ensuring that puberty is achieved in advance of 14 mo of age is critical. This allows heifers to calve as 2 year olds and optimizes lifetime efficiency. Feeding diets that promote elevated BW gain during the prepubertal period has been the primary strategy for achieving these end-points. Based on research conducted in our laboratories and others, it appears that the interval between approximately 4 and 7 mo of age (juvenile period) is a critical window for metabolically programming the neuroendocrine axis to achieve targeted reproductive maturation in heifers. By focusing on nutritionally mediated changes in the hypothalamus, we have been able to characterize several structural and functional modifications in hypothalamic pathways that respond to high-energy diets during this period. These include the differential expression of several genes (NPY, AGRP, POMC, and GHR) within the arcuate nucleus, a reduction in NPY innervation of GnRH neurons, decreased concentrations of central NPY, and increased innervation of kisspeptin neurons by αMSH. These alterations are consistent with the hypothesis that accelerated growth during the juvenile period, resulting in increased circulating leptin, leads to decreased inhibition and accelerated excitation of GnRH neurons. Novel nutritional and managerial approaches for optimizing growth during sensitive periods of infantile and juvenile development are required in order for fundamental biology to reach practical translation. These approaches must facilitate nutritional imprinting of the brain during early calfhood, while minimizing feeding costs, optimizing the consistent establishment of estrous cycles by 11 to 12 mo of age, and avoiding precocious puberty or disrupted mammary gland development. Our recent studies indicate that this may be achieved by exposing heifers to a stair-step nutritional regimen. However, a role for the maternal metabolic environment in heifer offspring responses to postnatal diets may also be operative. If confirmed, successful managerial strategies will also include the pregnant dam (USDA-NIFA grants 2009-65203-05678 and 2013-67015-20960).

Key Words: heifer, programming, puberty

5 Future reproduction in gilts and boars is affected prenatally by sow management and early in life by management conditions to which the developing swine are exposed. Mark J. Estienne*, *Virginia Tech, Blacksburg, VA.*

Applied research at Virginia Tech has focused on effects of pre- or post-natal conditions on reproduction in adults. In utero, swine fetuses can be programmed as a consequence of intrauterine growth retardation (IUGR) caused by insufficient uterine capacity. Although negative effects of IUGR on postnatal growth are well documented, possible reproductive effects have been less studied. Preliminary work from our laboratory, however, showed that low BW boars had poorer libido and semen quality than high BW boars; in gilts, age at puberty was negatively correlated with pig BW. It is becoming apparent that fetuses can also be programmed by management of the gestating sow. For example, we compared growth and reproductive characteristics of gilts farrowed by sows that were kept in individual crates throughout gestation, group pens throughout gestation, or individual crates for the first 30 d post-mating and then group pens for the remainder of pregnancy. During the last 4 wk of the grow-finish period, BW of gilts farrowed by females housed in crates throughout gestation was greater than BW of gilts in the other 2 groups. Also, the efficiency of feed conversion was greatest and last-rib backfat thickness the least, in gilts farrowed by females housed in crates throughout gestation. Interestingly, fewer gilts farrowed by females kept in crates throughout gestation reached puberty by 165 d of age compared with the other 2 groups. In intensively managed swine operations, there are many potential environmental stressors to which postnatal pigs are exposed early in life and this may affect future reproduction as well. For example, we determined the effects of crowding in the nursery on future reproduction and longevity in gilts. Reproductive performance during the second parity, including the number of pigs born alive was significantly greater for gilts each allowed 0.25 m^2 of floor space in the nursery compared with gilts restricted to 0.17 m^2. Research will continue to identify prenatal or early-in-life stressors and to develop management strategies for mitigating adverse effects on swine reproduction.

Key Words: gilts, boars, development

6 Our stolen figures: Using the process of sexual differentiation to think about endocrine-disrupting compounds and their effects on energy balance. Jill E. Schneider*, *Lehigh University, Bethlehem, PA.*

Reproductive processes (gametogenesis, hypothalamic-pituitary-gonadal function, and behavior) are masculinized or feminized during fetal development. At least some of these effects are determined during fetal development by androgens, estrogens, and glucocorticoids acting on cognate steroid receptors. These receptors, however, render reproductive development sensitive to endocrine-disrupting compounds that also act on the same receptors. Less well known is the fact that endocrine disruptors can alter energy balance (energy intake, storage, and expenditure). Recent evidence indicates that endocrine disruptors affect many individual processes known to contribute to obesity, including the gut microbiome, adipocyte differentiation, energy metabolism, ingestive behavior, and the tendency to accumulate adipose tissue in response to certain diets. Understanding effects of endocrine disruptors on energy balance will be aided by attention to the processes involved in sexual differentiation. This is because many energy-balancing traits are sexually dimorphic with the masculine phenotype most closely linked to metabolic diseases such as type II diabetes and heart disease. So far, it is clear that at least some endocrine disruptors have masculinizing effects via classical organizational effects on sexually dimorphic energy balancing traits during fetal development. In addition, we should expect endocrine disruptors to affect other defined mechanisms of sexual differentiation (e.g., sex chromosome action, aromatization, active feminization, and organizing actions at later periods of development, such as puberty). Investigators interested in effects of endocrine disruptors on peripheral metabolism often work in isolation from those interested in the effects of endocrine disruptors on ingestive behavior. In fact, changes in peripheral metabolism have organizational and activational effects on the neural circuitry that controls ingestive behavior. Together, these considerations demand a concerted multidisciplinary and integrative approach to the study of endocrine disruptors.

7 Environmentally induced epigenetic transgenerational inheritance of disease: Ancestral ghosts in your genome. Michael K. Skinner*, *Center for Reproductive Biology, School of Biological Sciences, Washington State University, Pullman, WA.*

Transgenerational effects of environmental toxicants significantly amplify the effect and health hazards of these compounds. One of the most sensitive periods to exposure is during embryonic gonadal sex determination when the germ line is undergoing epigenetic programming and DNA re-methylation. Previous studies have shown that endocrine disruptors can cause an increase in adult onset disease such as infertility, prostate, ovary and kidney disease, cancers and obesity. Interestingly, this effect is transgenerational (F_1, F_2, F_3, and F_4 generations) and hypothesized to be due to a permanent (imprinted) altered DNA methylation of the germ-line. The transgenerational epigenetic mechanism appears to involve the actions of an environmental compound at the time of sex determination to permanently alter the epigenetic (i.e., DNA methylation) programming of the germ line that then alters the transcriptomes of developing organs to induce disease susceptibility and development transgenerationally. A variety of different environmental compounds have been shown to induce this epigenetic transgenerational inheritance of disease including: fungicide vinclozolin, plastics BPA and phthalates, pesticides, DDT, dioxin and hydrocarbons. The suggestion that environmental factors can reprogram the germ line to induce epigenetic transgenerational inheritance of disease and phenotypic variation is a new paradigm in disease etiology that is also relevant to other areas of biology such as evolution.

8 Environmental effects on programming of reproductive behavior. Frederick vom Saal*, *University of Missouri-Columbia, Columbia, MO.*

Fetal development is a period of heightened sensitivity to hormones that regulate the differentiation of tissues. An example showing that very small differences in testosterone (T) and estradiol (E_2) during fetal life can lead to changes in the life history of males and females is the intrauterine position phenomenon or IUP. Developing between fetuses of the same or opposite sex in species in which there are multiple fetuses (polytocous species) results in very small differences in fetal serum T and E_2 and differences in the development of tissues, including the brain, responsive to these sex steroids. For example, in mice, 2F males (located in utero between 2 females) have elevated serum E_2 during fetal life and in adulthood show an increase in sexual behaviors relative to 2M males (located between 2 males); 2M males have elevated serum T during fetal life and in adulthood are more aggressive than 2F males. Similarly, 2F female mice are more sexually attractive to males and more sexually receptive, but less aggressive, than their 2M female siblings. There are now numerous environmental chemicals that have been found to bind to estrogen receptors and disrupt normal estrogen signaling. The best studied of these estrogenic endocrine-disrupting chemicals is bisphenol A or BPA. Developmental exposure to BPA has been related to numerous changes in brain structure, function, and behavior in both males and females. Of great interest is the finding that the magnitude of the sex differences in some behaviors observed in untreated rats and mice is reduced or eliminated as a result of exposure to doses of BPA that are relevant to exposures experienced by humans based on biomonitoring studies. While there is less information regarding the effects of endocrine disrupting chemicals such as BPA in farm animals relative to rodents or humans, there is evidence for effects of fetal exposure to BPA on neuroendocrine function in sheep. There is also evidence for transgenerational transmission of altered phenotype, including behavior, caused by exposure to endocrine disrupting chemicals during the period of germ cell epigenetic programming.

Key Words: endocrine disruptor, bisphenol A, fetal programming

9 Potential effects of real life exposure to environmental contaminants on reproductive health. Neil P. Evans*[1], Michelle Bellingham[1], Corinne Cotinot[2], Stewart M. Rhind[3], Richard Sharpe[4], and Paul A. Fowler[5], *[1]College Medical Veterinary and Life Sciences, Institute of Biodiversity Animal Health & Comparative Medicine, University of Glasgow, Glasgow, UK, [2]INRA, 1198 Biologie du Developpement et Reproduction, Jouy en Josas, France, [3]James Hutton Institute, Aberdeen, UK, [4]Queens Medical Research Institute, MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK, [5]Institute of Medical Sciences, Division of Applied Medicine, University of Aberdeen, Aberdeen, UK.*

While much research has focused on the effects of individual chemical exposures on animal health, far less is known about the effects of exposure to the mixtures of chemicals often found within our environment, even though this is a more typical exposure pattern. Biosolids (processed human sewage sludge) contain low individual concentrations of an array of contaminants including heavy metals and organic pollutants [e.g., polycyclic aromatic hydrocarbons, polychlorinated biphenyls and polychlorinated dibenzo(p)dioxin and furan] and form the basis of our model with which to study the effects of exposure to mixtures of environmentally relevant concentrations of pollutants in a domestic animal, the sheep. Studies using this model have investigated the effects of developmental exposure to biosolids on a variety of reproductive endpoints, including GnRH, kisspeptin, and estradiol receptor expression within the hypothalamus, LH and estradiol receptor expression within the pituitary gland, and protein, mRNA, and gamete production within the gonads of male and female sheep. The studies suggest that exposure to biosolids in utero, via maternal exposure, has detrimental effects on the fetal hypothalamo-pituitary-gonadal axis that could affect subsequent fertility. Studies with adult animals, also exposed during fetal life, suggest long-term effects of environmental chemical exposure on the reproductive axis. Investigation of lambs born to ewes grazed on biosolid-treated pastures (1) throughout life, (2) up until gestation, or (3) only during gestation have shown that some effects of environmental chemicals (relative to unexposed controls) may be more pronounced when exposure is acute, or that physiological compensation may occur when exposure is prolonged. Overall, the results of this study question the reliance on no observed adverse effects levels, with regard to chemical safety, when chemical exposure normally occurs as complex mixtures. The results suggest that developmental chemical exposure may affect the hypothalamo-pituitary-gonadal axis at a variety of levels, although whether the effects are driven by central effects or occur at each organ studied remains to be determined. [Wellcome Trust grant 080338].

Key Words: endocrine-disrupting chemicals, environmental contamination, ruminant