

Fetal programming of reproduction, what we know and how we manage it

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Introduction

For the purposes of this paper, fetal programming will cover developmental and nutritional programming both before and after birth. Developmental programming is defined as changes in anatomical structure and/or physiology that result from differences in gene function instead of variation in DNA sequence of the gene. These changes in gene function are due to epigenetic modifications to the genome that change the rate of transcription and translation of the genes, resulting in differences in the abundance of the proteins produced. Therefore, the “output of product” controlled by a gene may be increased or decreased, but the structure of that product will not be changed (Figure 1). Fetal programming implies that these mechanisms are set before birth; however, there is evidence that epigenetic modifications continue to take place after birth. Even between identical twins, environmental factors (e.g., nutrition, disease, or stress) encountered during a lifetime can change the epigenetic modifications to the genome later in life, resulting in changes in promoter (e.g., the switch that turns a gene on or off) methylation, histone acetylation, and microRNA (miRNA) profiles that can alter the abundance of protein produced (Fraga et al., 2005; Sinclair et al., 2016; Triantaphyllopoulos et al., 2016). While the sequence of DNA is identical within the twin pairs, the transcription and translation of those genes into proteins can be vastly different, resulting in very different phenotypes and physiological responses later in life between these two genetically identical individuals. Animal science is in its infancy in understanding how developmental programming can alter the epigenome and how we can control developmental programming to improve production efficiency. As we learn more about the mechanisms involved, we will have powerful tools for controlling function of the genome to target animals toward their niche in the production system.

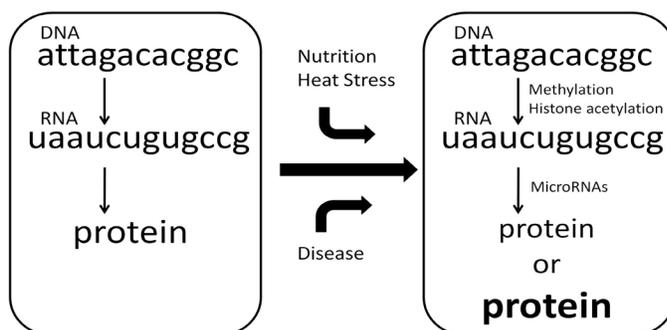


Figure 1. Environmental factors can change the “output of product” by epigenetic mechanisms without changing the sequence of the DNA.

Influence of developmental programming on target organs

Data exist to demonstrate developmental programming affects muscle, fat, mammary gland, hypothalamus, immune system, ovary, and uterus during different stages in the production cycle in a sex specific manner (Table 1); however, epigenetic modification have not yet been demonstrated clearly in all these cases (Sinclair et al., 2016; Triantaphyllopoulos et al., 2016). Studies of epigenetic regulation of the casein gene provide evidence of impacts of hormonal milieu, nutritional status, and health status on methylation in the promoter region in association with changes in casein transcript abundance in the mammary gland (Singh et al., 2012). Impacts of maternal nutrition on muscle development and tenderness in steer progeny have been reported (Du et al., 2010; Underwood et al., 2010), and a recent study demonstrated that applying different levels of maternal nutrition in the third trimester of gestation resulted in different miRNA profiles in the longissimus muscles of the steer progeny (Moisá et al., 2016). These changes in miRNA profiles were proposed to result in changes in intramuscular fat development and deposition. Additionally, metabolic imprinting during the growing phase in early weaned steers resulted in improved marbling (Scheffler et al., 2014). Thus, it seems possible to regulate carcass traits by strategic feeding of the dam during gestation or by strategic feeding of the steer during the growing phase. Finally, effects of developmental programming have been observed at the level of the bovine ovary, resulting in changes in the number of follicles that a heifer has. The changes that occur in female reproductive function seem to be dependent upon the developmental stage at which the programming event occurs. Different effects have been reported based upon programming events prior to conception, during early gestation, during late gestation, and during the peri-pubertal period. If we can understand the opportunities available in each of these windows, we may be able to harness the mechanisms involved to improve production efficiency.

Table 1. Targets influenced by developmental programming and the stage of life when they can be impacted.

	Developmental Stage		
	Fetus	Growing	Mature
	Fat♂	Intramuscular fat♂	Growing oocytes♀
	Immune system♂	Mammary cells♀	Mammary cells♀
	Muscle♂	Ovarian reserve♀	
	Ovary♀	Uterus♀	
	Uterus♀		

♂Steers

♀Heifers or cows

The ovarian reserve

A large portion of our team's research has focused on understanding how developmental programming influences the ovaries and the reproductive axis in replacement heifers. A heifer is born with approximately 100,000 oocytes (i.e., eggs) in her combined ovaries (Erickson, 1966; Fortune et al., 2013; Cushman et al., 2015b). These provide the germ cells (i.e., eggs) that she has for her entire reproductive lifespan (e.g., the ovarian reserve), and depletion of these germ cells is the primary mechanism leading to reproductive senescence in mammalian females. The majority of oocytes are located in dormant primordial follicles, and the process by which they enter the growing pool is known as activation (Fortune et al., 2000). The number of follicles that develop to sizes that can be detected by ultrasonography in heifers and cows is related positively to the size of the ovarian reserve (Cushman et al., 1999; Ireland et al., 2008).

Research has demonstrated a positive influence of the number of follicles in the ovary on fertility (Cushman et al., 2009), response to exogenous gonadotropins (Cushman et al., 1999; Singh et al., 2004), and earlier calving during the calving season (Mossa et al., 2012; Cushman et al., 2014b; McNeel and Cushman, 2015). Removal of the ovaries for histological evaluation is not acceptable in a production setting.

Therefore, the best method we have to evaluate ovarian reserve in heifers is ultrasonography to count the number of antral follicles (Cushman et al., 2015a). There is a positive relationship between the number of antral follicles and the number of primordial follicles. This strategy is used also in women to identify fertility issues and to determine the approach of menopause. Age at menopause has an heritability of 0.70 (de Bruin et al., 2001), and there is a genetic disorder known as premature ovarian failure that leads to depletion of the primordial follicles before age 40 and early onset of menopause (Chapman et al., 2015).

Although the heritability of most reproductive traits is low, those expressed early in life, especially antral follicle count, appear to have a relatively greater heritability (Cushman et al., 2014a), and, therefore, a greater potential for genomic applications (Figure 2). Over several studies, heritability of antral follicle count has been reported to average about 0.40 (Snelling et al., 2012; Walsh et al., 2014). Within dairy cows with greater response to exogenous gonadotropins (an indirect measure of a larger ovarian reserve), there was a positive genetic correlation with daughter pregnancy rates (Jaton et al., 2016). Collectively, these data indicate that fertility and reproductive longevity can be improved by genomic selection for the size of the ovarian reserve; however, a number of studies have demonstrated that developmental programming can increase or decrease of size of the ovarian reserve, both prenatally and after birth. This indicates that, beyond genomic selection, developmental programming and targeted feeding could be used to modify the epigenome to increase the size of the ovarian reserve to improve reproductive performance in beef cows. By combining molecular genetics to identify chromosomal regions influencing antral follicle count with functional genomics, we should be able to identify targets of epigenetic management that could be harnessed to improve fertility and reproductive longevity in beef heifers.

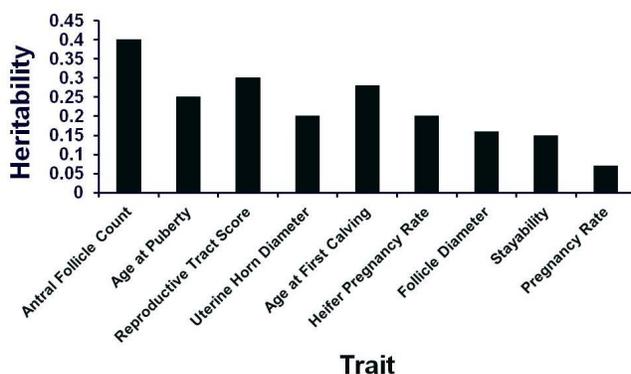


Figure 2. Average heritability of reproductive traits in beef cows. In general, those that are expressed earlier in life have a greater heritability than those expressed later in life.

Impacts on the developing oocytes

The time necessary for an activated primary follicle to grow to a Graafian follicle and ovulate has been estimated to be about 100 days (Lussier et al., 1987). During this time, the follicle and oocyte within are impacted by environmental factors such as health and nutrient status of the cow (Britt, 1992; Leroy et al., 2015). Physical connections between the cumulus cells and the oocyte allow bi-directional communication that can translate environmental stresses to the level of the oocyte. Research from Claude Robert's laboratory has demonstrated that RNAs can move back and forth between the oocyte and the cumulus

cells (Macaulay et al., 2014), and that long non-coding RNAs that exist in the oocyte can alter protein production during early embryonic development (Caballero et al., 2014). This is especially relevant during the post-partum period when the negative energy balance of the cow may impact follicle development and quality of the oocytes in growing secondary and antral follicles.

In 1992, Britt hypothesized that negative energy balance during the early post-partum period in dairy cows was altering the epigenetic machinery and competence of the developing oocytes (Britt, 1992). The Britt Hypothesis was supported by a study that demonstrated that preantral follicles harvested from dairy cows in the early post-partum period grew more slowly in culture and resulted in a lower percentage of morphologically normal follicles (Figueiredo et al., 1994). The fact that this may translate to decreased oocyte competence and poor early embryonic development was supported by a study that demonstrated decreased pregnancy likelihood after timed artificial insemination in dairy cows that suffered greater condition loss in the first three weeks post-partum (Carvalho et al., 2014). There may be broader implications to these alterations in oocyte competence, because they could alter development without resulting in early embryonic mortality. This could result in programmed changes in the physiology of the progeny that do not manifest themselves until much later in life. Overall, this situation seems more likely in dairy cows with the extreme negative energy balances associated with milk production; however, no one has examined these effects in post-partum beef cows. Additionally, post-partum beef cows would still be susceptible to immunological stresses and heat stresses that could alter the epigenome in growing oocytes with potential long-term impacts on performance of the progeny.

Impacts of nutrient status during gestation on reproductive capacity of female progeny

Fetal development is influenced differently by maternal nutrient intake at various stages of gestation. A long standing debate is whether the observed effects are due to differences in energy intake or differences in protein intake, but in most studies this is difficult to distinguish. Decreased nutrient intake among pregnant heifers fed 60% of maintenance during early gestation resulted in daughters with decreased numbers of antral follicles at a year of age (Mossa et al., 2013). This indicates that the fertility and reproductive longevity of those daughters might be impacted by this nutritional insult to the dam, but there are no scientific reports to verify this concept. When maternal nutrient intake was increased to dairy cows beginning at 60 days of gestation, daughters had fewer primordial follicles and increased numbers of antral follicles, indicating that primordial follicle activation and follicle growth to the antral stage had been stimulated by the increased maternal nutrient intake (Weller et al., 2016). Again, this might suggest that those daughters will have decreased reproductive longevity due to a smaller starting ovarian reserve, but those data are yet to be reported.

High protein diets during early gestation can have negative impacts on daughter follicle numbers as well. Sullivan et al. (2009) reported that daughters of cows fed a ration with greater than 200% NRC requirements for crude protein during the first or second trimester had decreased numbers of primordial follicles at 2 years of age. The authors proposed that increased plasma urea may have caused the nutritional insult that changed the morphology of the developing ovaries. It seems possible that oogonial proliferation could have been slowed in this period, but, no studies have examined the mechanisms contributing to this decrease in the size of the ovarian reserve.

Overall, nutritional insults in early gestation, such as drought, could decrease the size of the ovarian reserve in daughters. In sheep, intrauterine growth restriction during the third trimester decreased primordial follicle numbers (Da Silva et al., 2002; 2003), indicating that there may be mechanisms to increase the rate of decline of germ cell numbers during late gestation. Thus, the alternative that there could be mechanisms to slow the rate of decline should also be true. Protein supplementation to cows during the third trimester resulted in female progeny that conceived earlier in their first breeding season (Martin et al., 2007).

Therefore, we hypothesized that this was due to an increase in antral follicle numbers, and to test this hypothesis, we provided mature cows with 125% of maintenance requirements during the third trimester in hopes of increasing the number of follicles in the daughters (Cushman et al., 2014b). There was no influence on age at puberty or antral follicle numbers in the daughters, but the daughters of cows provided extra energy had greater conception rates during the first 3 weeks of their first breeding season, resulting in a significantly earlier calving date. In a similar study, Gunn et al. (2015) improved the nutrient status of beef cows in the third trimester by providing a distiller's grain supplement. The daughters had improved conception to a timed artificial insemination protocol compared to controls. Again, there was no difference in age at puberty or the number of antral follicles detectable by ultrasonography. It remains possible, however, that the change in number of antral follicle number was below the sensitivity of detection by ultrasonography, because Weller et al. (2016) observed microscopic increases in antral follicle numbers in daughters of cows provided energy supplementation during gestation. Alternatively, there may be changes in uterine function that contribute to the improved first service conception rates in these daughters.

From these studies it is clear that maternal nutrient intake throughout gestation may alter the structure and/or function of reproductive organs in female progeny. It seems that it should be possible to increase primordial follicle numbers in heifers if they are exposed in utero to the correct nutritional stimulation during the period of oogonial proliferation; however, thus far it has only been demonstrated that changes in maternal energy or protein intake negatively impact daughter germ cell numbers. This implies that a period of drought during early gestation for range beef cows could result in daughters with decreased reproductive capacity. The question remains whether a nutritional intervention later in gestation could reverse this decrease in germ cell number by slowing the rate of loss of germ cells in the third trimester, but thus far we have been unsuccessful at such a manipulation of the ovary.

Impacts of nutrient status during the peri-pubertal period on reproductive capacity

In rats, decreased nutrient intake in the peri-pubertal period resulted in an increase in the number of primordial follicles (Wang et al., 2014). This led us to investigate influence of caloric intake during the peri-pubertal period on primordial follicle numbers in beef heifers. Heifers fed to gain 0.4 to 0.5 kg/day between 8 and 11 months of age and then fed to gain 1.2 kg/day from 11 to 13 months (Stair-Step) of age had greater numbers of primordial follicles at 13 months of age than heifers fed to gain 1 kg/day from 8 to 13 months of age (Freetly et al., 2014; Amundson et al., 2015). Genomic analysis of the ovarian tissues identified increases in abundance of gene transcripts associated with follicle formation and growth. Data are still being generated at the U.S. Meat Animal Research Center to determine if this feeding regime improves lifetime productivity. Interestingly, Stair-Step heifers did wean heavier calves in their first 3 years, suggesting that the developing mammary tissue may also be influenced.

Effects of maternal age on antral follicle count in female progeny

Many factors influence our ability to program development of the ovarian reserve. For example, daughter antral follicle number is also influenced by maternal age. Walsh et al. (2014) reported that follicle numbers at a year of age were greater in dairy heifers born to mature cows than those born to heifers. This is probably due to differences in nutrient availability in utero, but it could be influenced by a lactocrine (milk endocrine) effect from the colostrum (Bartol and Bagnell, 2012). To our knowledge, lactocrine effects have not been reported in cattle. We have conducted research at the U.S. Meat Animal Research Center that shows differences in dam age between beef heifers with low or high numbers of antral follicles. It is challenging to dissect whether this is due to uterine or lactocrine effects. If maternal age alone can impact daughter follicle numbers, this indicates that mechanisms need to be understood clearly before they can be

manipulated and that fetal programming may very well interact with maternal age. This could mean that it will be easier to developmentally program size of the ovarian reserve in female progeny from heifers than from mature cows.

Epigenetic modifications as a result of assisted reproductive technologies

Production of embryos in vitro (either through in vitro fertilization or somatic cell nuclear transfer) can alter development resulting in early embryonic mortality, fetal death, or defects of the fetus and placenta (Farin et al., 2006). Among commonly observed difference is an increased birth weight, implying that nutrient availability in media during the first seven days is changing the growth trajectory of progeny. Fetal weights and ratio of secondary to primary muscle fiber numbers were increased in the semitendinosus muscle when in vitro produced fetuses were compared to in vivo produced fetuses at 222 days of gestation (Crosier et al., 2002). Myostatin gene transcript abundance in semitendinosus muscle was greater for in vitro produced fetuses than in vivo produced fetuses, indicating that function of genes involved in muscle development was altered. From data such as this, it has been hypothesized that epigenetic perturbations may be occurring as a result of in vitro embryo production (Farin et al., 2010). Understanding these epigenetic modifications would be a first step toward applying them to improve production efficiency.

Management strategies for applying epigenetics to beef cattle production

For many years, the goal of feeding strategies for developing replacement heifers has focused on minimizing inputs while insuring that the heifers attain puberty before their first breeding season. With incorporation of developmental programming, it seems likely that feeding strategies could play greater roles in how we manage and develop replacement heifers. Thus, a drought resulting in nutrient deficiency during the first trimester of pregnancy could send developing female progeny on a trajectory towards decreased reproductive capacity. If we understand this and place the developing heifers on a Stair-Step protocol we might be able to slow the loss of primordial follicles during the first year of life and improve their reproductive capacity. In theory, we might still be able to develop interventions during the third trimester of pregnancy that increase germ cell numbers at birth.

Such strategies need not be limited to replacement heifers. Targeted feeding suggests that we could use developmental programming to create animals better adapted for their niche in the production system (e.g., more fertile replacement heifers or steers with increased marbling), but this type of management system requires planning and more intensive management. Responses differ due to sex of the progeny, age of the dam, and stage of life when the programming event occurs (Table 1). Therefore, assisted reproductive technologies become more important because synchronization of estrus and artificial insemination are needed to better control the stage of gestation and in the case of sex-specific prenatal responses allow for use of sexed-semen.

Epigenetic modifications that occur with in vitro produced embryos need not be a concern, and in even more intensive management systems might be applied in a positive manner to target progeny toward their niche in the production system. Before we can attain this degree of accuracy in precision animal management, we will require a much better understanding of the epigenetic machinery and how it is regulated. In the future, management of the epigenome will become as important as choosing the right bull for the next breeding season.

References

- Amundson, O. L., T. H. Fountain, E. L. Larimore, B. N. Richardson, A. K. McNeel, E. C. Wright, D. H. Keisler, R. A. Cushman, G. A. Perry, and H. C. Freetly. 2015. Postweaning nutritional programming of ovarian development in beef heifers. *J. Anim. Sci.* 93:5232-9.
- Bartol, F. F., and C. A. Bagnell. 2012. Lactocrine programming of female reproductive tract development: Environmental connections to the reproductive continuum. *Mol. Cell. Endocrinol.* 354:16-21.
- Britt, J. H. 1992. Impacts of early postpartum metabolism on follicular development and Fertility. *Bovine Practitioner* 24:39-43.
- Caballero, J., I. Gilbert, E. Fournier, D. Gagné, S. Scantland, A. Macaulay, and C. Robert. 2014. Exploring the function of long non-coding RNA in the development of bovine early embryos. *Reprod. Fertil. Dev.* 27:40-52.
- Carvalho, P. D., A. H. Souza, M. C. Amundson, K. S. Hackbart, M. J. Fuenzalida, M. M. Herlihy, H. Ayres, A. R. Dresch, L. M. Vieira, J. N. Guenther, R. R. Grummer, P. M. Fricke, R. D. Shaver, and M. C. Wiltbank. 2014. Relationships between fertility and postpartum changes in body condition and body weight in lactating dairy cows. *J. Dairy Sci.* 97:3666-83.
- Chapman, C., L. Cree, and A. N. Shelling. 2015. The genetics of premature ovarian failure: current perspectives. *Int. J. Womens Health* 7:799-810.
- Crosier, A. E., C. E. Farin, K. F. Rodriguez, P. Blondin, J. E. Alexander, and P. W. Farin. 2002. Development of skeletal muscle and expression of candidate genes in bovine fetuses from embryos produced in vivo or in vitro. *Biol. Reprod.* 67:401-8.
- Cushman, R. A., M. F. Allan, L. A. Kuehn, W. M. Snelling, A. S. Cupp, and H. C. Freetly. 2009. Evaluation of antral follicle count and ovarian morphology in crossbred beef cows: Investigation of influence of stage of the estrous cycle, age, and birth weight. *J. Anim. Sci.* 87:1971-1980.
- Cushman, R. A., J. C. DeSouza, V. S. Hedgpeth, and J. H. Britt. 1999. Superovulatory response of one ovary is related to the micro- and macroscopic population of follicles in the contralateral ovary of the cow. *Biol. Reprod.* 60:349-354.
- Cushman, R. A., T. G. McDanel, L. A. Kuehn, W. M. Snelling, and D. Nonneman. 2014a. Incorporation of genetic technologies associated with applied reproductive technologies to enhance world food production. *Adv. Exp. Med. Biol.* 752:77-96.
- Cushman, R. A., A. K. McNeel, and H. C. Freetly. 2014b. The impact of cow nutrient status during the second and third trimester on age at puberty, antral follicle count, and fertility of daughters. *Livestock Sci.* 162:252-258.
- Cushman, R. A., A. K. McNeel, J. C. Souza, and J. H. Britt. 2015a. Applying ultrasonographic evaluation of antral follicle count to improve reproductive management in heifers. *Clin. Theriogenology* 7:223-227.
- Cushman, R. A., A. K. McNeel, J. C. Souza, S. E. Echterkamp, J. H. Britt, and H. C. Freetly. 2015b. Mechanisms influencing establishment of the ovarian reserve in heifers. *Clin. Theriogenology* 7:229-233.
- Da Silva, P., R. P. Aitken, S. M. Rhind, P. A. Racey, and J. M. Wallace. 2002. Impact of maternal nutrition during pregnancy on pituitary gonadotrophin gene expression and ovarian development in growth-restricted and normally grown late gestation sheep fetuses. *Reproduction* 123:769-77.
- Da Silva, P., R. P. Aitken, S. M. Rhind, P. A. Racey, and J. M. Wallace. 2003. Effect of maternal overnutrition during pregnancy on pituitary gonadotrophin gene expression and gonadal morphology in female and male foetal sheep at day 103 of gestation. *Placenta* 24:248-57.

- de Bruin, J. P., H. Bovenhuis, P. A. van Noord, P. L. Pearson, J. A. van Arendonk, E. R. te Velde, W. W. Kuurman, and M. Dorland. 2001. The role of genetic factors in age at natural menopause. *Hum. Reprod.* 16:2014-8.
- Du, M., J. Tong, J. Zhao, K. R. Underwood, M. Zhu, S. P. Ford, and P. W. Nathanielsz. 2010. Fetal programming of skeletal muscle development in ruminant animals. *J. Anim. Sci.* 88:E51-60.
- Erickson, B. H. 1966. Development and senescence of the postnatal bovine ovary. *J. Anim. Sci.* 25:800-805.
- Farin, C. E., W. T. Farmer, and P. W. Farin. 2010. Pregnancy recognition and abnormal offspring syndrome in cattle. *Reprod. Fertil. Dev.* 22:75-87.
- Farin, P. W., J. A. Piedrahita, and C. E. Farin. 2006. Errors in development of fetuses and placentas from in vitro-produced bovine embryos. *Theriogenology* 65:178-91.
- Figueiredo, J. R., S. C. J. Hulshof, R. van den Hurk, M. M. Bevers, M. Thiry, B. Nusgens, and J. F. Beckers. 1994. The physiological status of ovarian donor affects in vitro development of isolated bovine preantral follicles. *Theriogenology* 42:1303-1310.
- Fortune, J. E., R. A. Cushman, C. M. Wahl, and S. Kito. 2000. The primordial to primary follicle transition. *Mol. Cell. Endocrinol.* 163:53-60.
- Fortune, J. E., M. Y. Yang, J. J. Allen, and S. L. Herrick. 2013. Triennial Reproduction Symposium: the ovarian follicular reserve in cattle: what regulates its formation and size? *J. Anim. Sci.* 91:3041-50.
- Fraga, M. F., E. Ballestar, M. F. Paz, S. Ropero, F. Setien, M. L. Ballestar, D. Heine-Suner, J. C. Cigudosa, M. Urioste, J. Benitez, M. Boix-Chornet, A. Sanchez-Aguilera, C. Ling, E. Carlsson, P. Poulsen, A. Vaag, Z. Stephan, T. D. Spector, Y. Z. Wu, C. Plass, and M. Esteller. 2005. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc. Natl. Acad. Sci U S A* 102:10604-9.
- Freetly, H. C., K. A. Vonnahme, A. K. McNeel, L. E. Camacho, O. L. Amundson, E. D. Forbes, C. A. Lents, and R. A. Cushman. 2014. The consequence of level of nutrition on heifer ovarian and mammary development. *J. Anim. Sci.* 92:5437-43.
- Gunn, P. J., J. P. Schoonmaker, R. P. Lemenager, and G. A. Bridges. 2015. Feeding distiller's grains as an energy source to gestating and lactating beef heifers: Impact on female progeny growth, puberty attainment, and reproductive processes. *J. Anim. Sci.* 93:746-757.
- Ireland, J. L., D. Scheetz, F. Jimenez-Krassel, A. P. Themmen, F. Ward, P. Lonergan, G. W. Smith, G. I. Perez, A. C. Evans, and J. J. Ireland. 2008. Antral follicle count reliably predicts number of morphologically healthy oocytes and follicles in ovaries of young adult cattle. *Biol. Reprod.* 79:1219-25.
- Jaton, C., A. Koeck, M. Sargolzaei, F. Malchiodi, C. A. Price, F. S. Schenkel, and F. Miglior. 2016. Genetic analysis of superovulatory response of Holstein cows in Canada. *J. Dairy Sci.* 99:3612-23.
- Leroy, J. L., S. D. Valckx, L. Jordaens, J. De Bie, K. L. Desmet, V. Van Hoeck, J. H. Britt, W. F. Marei, and P. E. Bols. 2015. Nutrition and maternal metabolic health in relation to oocyte and embryo quality: critical views on what we learned from the dairy cow model. *Reprod. Fertil. Dev.* 27:693-703.
- Lussier, J. G., P. Matton, and J. J. Dufour. 1987. Growth rates of follicles in the ovary of the cow. *J. Reprod. Fertil.* 81:301-307.
- Macaulay, A. D., I. Gilbert, J. Caballero, R. Barreto, E. Fournier, P. Tossou, M. A. Sirard, H. J. Clarke, E. W. Khandjian, F. J. Richard, P. Hyttel, and C. Robert. 2014. The gametic synapse: RNA transfer to the bovine oocyte. *Biol. Reprod.* 91:90.
- Martin, J. L., K. A. Vonnahme, D. C. Adams, G. P. Lardy, and R. N. Funston. 2007. Effects of dam nutrition on growth and reproductive performance of heifer calves. *J. Anim. Sci.* 85:841-7.

- McNeel, A. K., and R. A. Cushman. 2015. Influence of puberty and antral follicle count on calving day in crossbred beef heifers. *Theriogenology* 84:1061-1066.
- Moisá, S. J., D. W. Shike, L. Shoup, and J. J. Loo. 2016. Maternal Plane of Nutrition During Late-Gestation and Weaning Age Alter Steer Calf Longissimus Muscle Adipogenic MicroRNA and Target Gene Expression. *Lipids* 51:123-38.
- Mossa, F., F. Carter, S. W. Walsh, D. A. Kenny, G. W. Smith, J. L. Ireland, T. B. Hildebrandt, P. Lonergan, J. J. Ireland, and A. C. Evans. 2013. Maternal undernutrition in cows impairs ovarian and cardiovascular systems in their offspring. *Biol. Reprod.* 88:92.
- Mossa, F., S. W. Walsh, S. T. Butler, D. P. Berry, F. Carter, P. Lonergan, G. W. Smith, J. J. Ireland, and A. C. Evans. 2012. Low numbers of ovarian follicles ≥ 3 mm in diameter are associated with low fertility in dairy cows. *J. Dairy Sci.* 95:2355-61.
- Scheffler, J. M., M. A. McCann, S. P. Greiner, H. Jiang, M. D. Hanigan, G. A. Bridges, S. L. Lake, and D. E. Gerrard. 2014. Early metabolic imprinting events increase marbling scores in fed cattle. *J. Anim. Sci.* 92:320-4.
- Sinclair, K. D., K. M. Rutherford, J. M. Wallace, J. M. Brameld, R. Stoger, R. Alberio, D. Sweetman, D. S. Gardner, V. E. Perry, C. L. Adam, C. J. Ashworth, J. E. Robinson, and C. M. Dwyer. 2016. Epigenetics and developmental programming of welfare and production traits in farm animals. *Reprod. Fertil. Dev.*
- Singh, J., M. Dominguez, R. Jaiswal, and G. P. Adams. 2004. A simple ultrasound test to predict the superstimulatory response in cattle. *Theriogenology* 62:227-43.
- Singh, K., A. J. Molenaar, K. M. Swanson, B. Gudex, J. A. Arias, R. A. Erdman, and K. Stelwagen. 2012. Epigenetics: a possible role in acute and transgenerational regulation of dairy cow milk production. *Animal* 6:375-81.
- Snelling, W. M., R. A. Cushman, M. R. Fortes, A. Reverter, G. L. Bennett, J. W. Keele, L. A. Kuehn, T. G. McDanel, R. M. Thallman, and M. G. Thomas. 2012. Physiology and Endocrinology Symposium: How single nucleotide polymorphism chips will advance our knowledge of factors controlling puberty and aid in selecting replacement beef females. *J. Anim. Sci.* 90:1152-65.
- Sullivan, T. M., G. C. Micke, R. M. Greer, H. F. Irving-Rodgers, R. J. Rodgers, and V. E. Perry. 2009. Dietary manipulation of *Bos indicus* x heifers during gestation affects the reproductive development of their heifer calves. *Reprod. Fertil. Dev.* 21:773-84.
- Triantaphyllopoulos, K. A., I. Ikonopopoulos, and A. J. Bannister. 2016. Epigenetics and inheritance of phenotype variation in livestock. *Epigenetics Chromatin* 9:31.
- Underwood, K. R., J. F. Tong, P. L. Price, A. J. Roberts, E. E. Grings, B. W. Hess, W. J. Means, and M. Du. 2010. Nutrition during mid to late gestation affects growth, adipose tissue deposition, and tenderness in cross-bred beef steers. *Meat Sci.* 86:588-93.
- Walsh, S. W., F. Mossa, S. T. Butler, D. P. Berry, D. Scheetz, F. Jimenez-Krassel, R. J. Tempelman, F. Carter, P. Lonergan, A. C. Evans, and J. J. Ireland. 2014. Heritability and impact of environmental effects during pregnancy on antral follicle count in cattle. *J. Dairy Sci.* 97:4503-11.
- Wang, N., L. L. Luo, J. J. Xu, M. Y. Xu, X. M. Zhang, X. L. Zhou, W. J. Liu, and Y. C. Fu. 2014. Obesity accelerates ovarian follicle development and follicle loss in rats. *Metabolism* 63:94-103.
- Weller, M. M., M. R. Fortes, M. I. Marcondes, P. P. Rotta, T. R. Gionbeli, S. C. Valadares Filho, M. M. Campos, F. F. Silva, W. Silva, S. Moore, and S. E. Guimaraes. 2016. Effect of maternal nutrition and days of gestation on pituitary gland and gonadal gene expression in cattle. *J. Dairy Sci.* 99:3056-71.