Effect of Prenatal Programming on Heifer Development

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KEYWORDS

• Fetal programming • Maternal nutrition • Epigenetic modification • Beef cow

KEY POINTS

- Two main mechanisms responsible for fetal programming include DNA methylation and histone modifications.
- Alterations in the genome can be passed through multiple generations.
- Gestational nutrition can affect placental efficiency, fetal organ development, and progeny weaning body weight.
- Late-gestation protein supplementation can decrease heifer progeny age at puberty and increase reproductive efficiency.
- Maternal environment (nutrition, age, physiologic status) can program progeny heifer growth and reproductive performance.

INTRODUCTION

There are several characteristics suggesting the "ideal" beef cow. First, she calves at 2 years of age, does not require human intervention to calve or assistance in nursing her calf, maintains a 365-day calving interval, and weans a marketable calf each year. Furthermore, this animal must remain structurally sound, be able to graze the forages provided in her area, and be tolerant of environmental stressors and disease.[1] Profitability of beef cattle producers is tied directly to the productive life span of mature cows. Heifer development costs are recovered through subsequent calf crops. Reproductive failure represents a major reason females leave the herd, affecting producers' ability to recoup heifer development costs. Nutrition plays a major role in all aspects of beef cattle productivity. Furthermore, it is suggested the fetus is rarely able to

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completely express its full genetic potential for growth, owing to insults caused by the maternal environment.[2]

The main factors influencing nutrient partitioning between the dam and fetus include age of the dam, number of fetuses, production demand, and environmental stress.[3] These factors play a critical role in programming the fetus for its future environment and available resources. Moreover, fetal programming reportedly affects neonatal mortality and morbidity, postnatal growth rate, body composition, health, and reproduction.[4]

EPIGENETIC MODIFICATIONS

Epigenetics is defined as heritable changes in gene expression resulting from alterations in chromatin structure but not DNA sequence. Two mechanisms known to be involved in causing epigenetic changes to the genome include DNA methylation and histone modification.[5] These processes regulate both the intensity and timing of gene expression during cell differentiation.[6,7] Current understanding of these genomic modifications has led to the hypothesis that epigenetics is a key mechanism allowing for phenotypic plasticity with regard to a fixed genotype.[7]

Human epidemiologic studies report associations between low birth body weight (BW) and adult disease. Researchers propose that a fetal programming mechanism occurs whereby environmental stimuli in utero affect fetal growth and health not only during gestation but also later in life.[8,9] Animal models that report intrauterine growth retardation caused by maternal undernutrition indicate altered organ and tissue development in utero.[10,11] These studies suggest modification of the growing fetus to allow environmental adaptation. Epigenetic modifications can result from internal, as well as external, stimuli,[12] thus allowing gene expression in the fetus to best fit with environmental stimulation.

To help explain the main events and processes linking dietary exposures to epigenetic marks and, later, health outcomes, Mathers and McKay[12] developed the 4 Rs of nutritional epigenomics. From this model, one learns that nutrition stimuli and other exposures are (1) received and (2) recorded by the genome. Exposures are also (3) remembered across successive cell generations, and finally, (4) revealed in altered gene expression, cell function, and overall health.[12]

DNA Methylation

Most mammalian DNA, including exons, intergenic DNA, and transposons, is methylated. Methylation sites are located at cytosine bases, followed by a guanosine (CpG).[13] Although most CpG sites are methylated, specific CpG-rich areas of the genome, known as CpG islands, are not methylated. These regions span the 5′ end of the regulatory region of a gene.[6] The pattern of CpG-island DNA methylation varies based on tissue type, and this variation likely results in the differing expression of genes in diverse tissues.[14]

The DNA methyltransferase (Dnmt) family of enzymes plays an important role in DNA methylation and, ultimately, embryonic development and survival. Dnmt1, Dnmt3a, and Dnmt3b catalyze cytosine methylation. Furthermore, Dnmt3a and Dnmt3b can establish methylation patterns on unmodified DNA, whereas Dnmt1 maintains these patterns[15] when DNA is duplicated before cell division. Dnmt-null mice die in early gestation,[16] and methyltransferase mutations can cause not only abnormal fetal growth but also immunodeficiency and brain abnormalities in humans.[17]

Methyltransferases use *S*-adenosylmethionine (SAM) as a methyl donor, and SAM can be directly influenced by diet. Methyl donors for SAM include choline, methionine,