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Programming health in humans and herds

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Introduction

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More than three decades ago, David Barker and colleagues reframed how we think about chronic disease risk across the life course. The classic "Barker hypothesis" proposed that conditions in utero, particularly those constraining fetal growth, leave durable biological imprints that shape susceptibility to cardiovascular and other metabolic diseases in later life. While research over the past decades has advance our understanding of how early-life environments perturb development, a central challenge remains on establishing clear cause and effect links between exposure and outcomes, defining sensitive windows, and identifying interventions that are both biologically sound and clinically realistic.

Large animal (livestock) models provide a particularly strong platform for translating this concept into mechanism. These animals are not simply "bigger" models. They are dual-purpose and dual-benefit systems that can be used to answer foundational DOHaD questions while simultaneously producing actionable knowledge for animal health and agricultural sustainability. A major theme in recent "One Health" discussions is that domesticated animals enable research that is relevant to both agriculture and biomedicine, often with methodological opportunities that are difficult to replicate in rodents, such as long gestational length, longitudinal sampling, and integrated physiological studies.

This themed issue "Fetal programming in livestock: a unique opportunity for advancing both translational DOHaD and animal agricultural research" was assembled to highlight exactly these strengths. It examines how prenatal and early postnatal environments shape development in livestock, and how these effects persist to influence later outcomes. The papers address key exposures and pathways relevant to both DOHaD and production systems, including maternal nutritional imbalance, heat stress–induced placental insufficiency and fetal growth restriction (FGR), and endocrine perturbations, with particular emphasis on glucocorticoid signaling. Together, the contributions highlight emerging mechanisms and identify intervention targets that are biologically grounded and practically relevant. The collection includes one original research article and a set of focused reviews.

The issue opens with an original research study showing that molecular programming can be evident before phenotypes are visible. Craner et al.[1] investigate whether maternal vitamin and mineral supplementation throughout gestation programs the neonatal jejunum in calves. Using RNA-seq, the study identifies 528 differentially expressed genes in the jejunal mucosa of calves born to supplemented versus control dams. The pathways are relevant to nutrient transport, lipid metabolism, and immune-associated processes. The key contribution of this paper is not that maternal micronutrient supply changes neonatal intestinal transcription, but that it offers a mechanistic insight for understanding how maternal management practices may shape early immune and absorptive function long before overt phenotypes become apparent.

Swanson et al.[2] review how maternal nutrition, including under- and over-nutrition, and targeted macro- and micronutrient supplementation, can program offspring development and lifetime performance in livestock. The authors emphasize the placenta as a central mediator, where nutritional perturbations can alter placental growth, vascularity, and blood flow. Mechanistically, the review highlights durable regulation through gene expression and epigenetic pathways (DNA methylation, histone marks, and non-coding RNAs), while emphasizing that evidence for transgenerational inheritance in livestock is emerging but still limited. The review concludes by underscoring the value of livestock as "dual-purpose" DOHaD models for both agricultural and biomedical insight and calls for more direct measures of uteroplacental nutrient delivery, fetal nutrient demand, and epigenetic regulation along with longitudinal assessment of long-term and intergenerational outcomes.

Zhao et al.[3] review how maternal heat stress during gestation progressively impairs placental growth that causes FGR and its associated fetal milieu of hypoxemia, hypoglycemia, and reduced anabolic hormone concentrations. They argue that skeletal muscle is a primary downstream target because of its large contribution to fetal mass and high energy demand. Drawing evidence primarily from chronically catheterized fetal sheep, the authors demonstrate that heat stress-induced placental insufficiency reduces skeletal muscle growth through lower satellite cell proliferation, smaller myofibers, and markedly reduced protein synthesis/protein accretion. Mechanistically, the review highlights mitochondrial dysfunction as a key constraint on muscle growth, evidenced by reduced oxidative phosphorylation, lower complex I activity, and inhibited pyruvate flux into the mitochondrial matrix. Finally, the authors evaluate emerging nutritional intervention strategies

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targeting IGF-1, insulin, amino acids, and especially correcting fetal hypoxemia and hypoglycemia. The authors conclude that single substrate supplementation often underperforms because constraints on growth are systemic and multifaceted, and that future work should prioritize integrated strategies that simultaneously support oxygen delivery and key nutrient substrates to meaningfully restore muscle growth in FGR offspring.

Two complementary reviews in this issue both focus on glucocorticoids as a core programming signal in DOHaD using livestock as a model. Both emphasize that glucocorticoids are essential for late-gestation maturation, but premature or excessive exposure, mainly due to maternal stress or complications, reduced placental 11βHSD2 barrier function, early fetal HPA activation, or synthetic antenatal steroids, can shift developmental trajectories with lasting effects.

Amanollahi et al.[4] focus on the fetal heart and the "double-edged" role of glucocorticoids in cardiometabolic programming. In normal pregnancy, there is a physiological rise in cortisol to support maturation. However, pregnancy complications, maternal stress, and clinical interventions can elevate glucocorticoids prematurely or excessively before the heart is developmentally prepared to benefit, potentially altering cardiometabolic pathways that influence later cardiovascular risk. The authors also discuss the cardiovascular consequences of antenatal synthetic glucocorticoids (betamethasone or dexamethasone), and emphasize that they cross the placenta and are not inactivated by placental 11βHSD2, which can increase fetal exposure. They summarize molecular evidence that antenatal glucocorticoids can downregulate cardiac glucocorticoid receptor (GR) abundance and disrupt the normal maturational shift toward fatty-acid metabolism. The authors conclude that, despite strong evidence that glucocorticoids shape cardiac maturation, the mechanistic link between prenatal glucocorticoid exposure and long-term cardiovascular outcomes remains incompletely defined.

Fowden et al.[5] extend the glucocorticoid theme from cardiac development to whole-body metabolism by asking how early-life glucocorticoid overexposure programs metabolic phenotype in livestock across fetal and postnatal life. The authors explicitly organize their review around prenatal metabolic effects and postnatal metabolic effects of early-life glucocorticoid exposure in livestock. Prenatally, they emphasize placental control of fetal exposure (11βHSD2) and show that sustained fetal cortisol elevations can reduce rates of umbilical (fetal) glucose uptake while increasing fetal glucogenic capacity. Postnatally, they discuss how early glucocorticoid exposure can shape metabolic phenotype beyond birth through persistent changes in tissue metabolism and endocrine regulation. They conclude by calling for better defined exposure windows and longitudinal follow-up in large-animal models, including sex effects and aging outcomes.

Antenatal steroids are widely used to reduce morbidity and mortality in preterm birth primarily via fetal lung maturation, but expanding use has also raised concern about broader impacts on fetal development. Carter et al.[6] bring clinical relevance directly into view by reviewing antenatal steroid exposures and potential off-target programming effects beyond pulmonary maturation. Their review argues that optimizing antenatal steroid use requires stronger evidence on organ system impacts (immune, cardiovascular, renal, and hepatic), improved patient selection, and dosing strategies informed by pharmacokinetics. Importantly, they highlight that livestock models, particularly sheep, are strong platforms for defining mechanistic understanding and informing translational decision making.

Last, but certainly not least, Meyer[7] presents evidence showing that the neonatal period is a critical window in which perinatal exposures and early postnatal environments both shape ruminant survival and productivity. Her review summarizes how maternal influences, especially energy and protein status in late gestation, shape not only fetal growth but also parturition difficulty, colostrum availability and composition, transfer of passive immunity and weaning performance. Finally, the author argues that programming effects attributed to gestation alone can be incomplete without considering early neonatal biology and management, and they call for research that integrates prenatal mechanisms with neonatal physiology and later-life performance measures.

Across these contributions, two cross-cutting themes emerge. First, across the nutrition and growth-restriction literature represented in this issue, the placenta repeatedly appears as a central mediator of fetal programming. Whether the initiating exposure is nutritional imbalance, heat stress, or endocrine disturbance, placental development, transport capacity, and endocrine function shape fetal access to oxygen and nutrient substrates. This underscores a practical point for intervention studies: when placental constraints are dominant, successful strategies may need to target not only substrate provision but also placental function, fetal oxidative capacity, and endocrine regulation. Second, endocrine signals remain central to both normal maturation and developmental programming. The glucocorticoid-focused reviews emphasize that cortisol is essential for late-gestation maturation, but premature or excessive exposure can redirect developmental trajectories with lasting cardiometabolic and metabolic consequences. The review on antenatal steroid therapy extends this perspective to clinical practice, where synthetic glucocorticoids provide clear benefits but may also influence developing organ systems beyond the lung. Together, they highlight strong dependence on dose, duration, and developmental stage. Importantly, all authors underscore the value of livestock models for defining windows of vulnerability, identifying organ-specific mechanisms, and informing safer intervention strategies.

This special issue of the Journal of Developmental Origins of Health and Disease aims to be a valuable resource for researchers interested in the mechanisms and consequences of fetal programming in livestock, and in how these models can strengthen the broader DOHaD framework. The contributing authors are leaders in their respective fields, and together the original research and reviews provide both depth and perspective across maternal nutrition, placental function, endocrine regulation, FGR, and neonatal adaptation. Importantly, these papers also make clear that major gaps remain, particularly in defining sensitive windows, optimizing therapeutic strategies to alleviate FGR, and evaluating long-term and intergenerational effects. We hope that articulating these unanswered questions will help sharpen priorities and stimulate the next generation of mechanistic and translational studies that improve both agricultural sustainability and lifelong health.

Competing interests. None.

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