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Long-Term Consequences of Adaptive Fetal Programming in Ruminant Livestock

*Allison N. Vautier and Caitlin N. Cadaret**

Department of Animal Sciences, Colorado State University, Fort Collins, CO, United States

Environmental perturbations during gestation can alter fetal development and postnatal animal performance. In humans, intrauterine growth restriction (IUGR) resulting from adaptive fetal programming is known as a leading cause of perinatal morbidity and mortality and predisposes offspring to metabolic disease, however, the prevalence and impact in livestock is not characterized as well. Multiple animal models have been developed as a proxy to determine mechanistic changes that underlie the postnatal phenotype resulting from these programming events in humans but have not been utilized as robustly in livestock. While the overall consequences are similar between models, the severity of the conditions appear to be dependent on type, timing, and duration of insult, indicating that some environmental insults are of more relevance to livestock production than others. Thus far, maternofetal stress during gestation has been shown to cause increased death loss, low birth weight, inefficient growth, and aberrant metabolism. A breadth of this data comes from the fetal ruminant collected near term or shortly thereafter, with fewer studies following these animals past weaning. Consequently, even less is known about how adaptive fetal programming impacts subsequent progeny. In this review, we summarize the current knowledge of the postnatal phenotype of livestock resulting from different models of fetal programming, with a focus on growth, metabolism, and reproductive efficiency. We further describe what is currently known about generational impacts of fetal programming in production systems, along with gaps and future directions to consider.

Keywords: *in utero*, intergenerational, nutrient restriction, postnatal, ruminant

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***Correspondence:**
Caitlin N. Cadaret
caitlin.cadaret@colostate.edu

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INTRODUCTION

Postnatal growth and performance of mammalian species is largely influenced by fetal growth and development, with deviations from normal resulting in modification of typical growth patterns and aberrant metabolism after birth. Hales and Barker (2001) first explained this phenomenon with their thrifty phenotype hypothesis in humans, that credits adaptive fetal responses aimed at sparing nutrients as the epidemiological explanation for postnatal metabolic dysfunction and adult disease. Since then, a concerted effort has been made to understand how external factors during gestation alter the *in utero* environment, resulting in adaptive fetal growth and function (Gluckman and Hanson, 2004; Flinn et al., 2020). When these responses are not corrected before birth, they will result in lifelong impacts, which is referred to as developmental or fetal programming. These adaptations frequently result in a condition known as intrauterine growth restriction (IUGR)

which remains the second leading cause of perinatal morbidity and mortality in humans (Alisi et al., 2011). Improved neonatal care for infants across the developed world, along with increased understanding of IUGR has led to decreased infant mortality in humans (Goldenberg and Culhane, 2007), however, the impacts and management of adaptive fetal programming in livestock species needs further understanding.

In production settings, fetal programming in livestock is likely the result of poor fetal nutrition during gestation. Common industry practices such as breeding peripubertal dams contributes to these environments, as this causes competitive allocation of nutrients between the fetus, placenta, and the still growing dam. Other production standards such as selection for milk yield or lamb prolificacy (Gootwine et al., 2007), the presence of multiple fetuses, poor pasture conditions, as well as environmental perturbations throughout gestational periods can also contribute to poor fetal nutrition (Redmer et al., 2004; Wu et al., 2004, 2006; Reynolds et al., 2010; Yates et al., 2018). Reduced energy reserves and decreased vigor at birth in conjunction with reduced birthweight leads to a significant disadvantage throughout the first few months of life (Dwyer et al., 2016). Similar to IUGR-born children, livestock experiencing compromised fetal growth are at increased risk of perinatal morbidity and mortality, while also being predisposed to metabolic and organ dysfunction (Brown et al., 2015), cardiovascular disease (Wu et al., 2006; Reynolds and Vonnahme, 2017) and poor body composition (De Blasio et al., 2007; Gibbs et al., 2019). Approximately 8% of products from the U.S. livestock industry are lost annually due to a lack of management techniques for low birthweight animals (Wu et al., 2006), necessitating further understanding of the etiology and long-term consequences of adaptive fetal growth. Current research in livestock largely focuses on perinatal mechanistic changes with fewer studies following the postnatal animal. Consequently, there is a gap in knowledge that falls after weaning and in the production and performance of subsequent generations. In this review, we highlight current knowledge regarding postnatal growth, metabolic, and reproductive consequences of adaptive fetal programming as seen in various ruminant models. We further present the limited knowledge of intergenerational programming in ruminants along with areas of focus for future research.

FETAL PROGRAMMING

Since the placenta is the sole mediator of nutrient transport between dam and fetus, developmental programming is often the result of placental insufficiency due to placental stunting (Cox and Marton, 2009). In livestock, placental stunting can occur as the result of environmental perturbations, poor nutritional management or illness leading to maternal stress that increases body temperature and repartitions blood flow away from the uterus (Wallace et al., 2005; Greenwood and Cafe, 2007). Impact on the placenta is dependent upon timing and duration of maternal insult (Painter et al., 2005; Van Eetvelde et al., 2016). Maternal stress maintained during early to mid-gestation, when peak placental growth is taking place, is more likely to cause placental stunting than during late gestation when it may instead lead to a direct fetal insult. As the disparity between fetal nutrient and oxygen requirements and those supplied by the placenta grows, the fetus will begin to elicit a series of responses aimed at sparing nutrients for vital organs (Hales and Barker, 1992, 2001; Redmer et al., 2004; Poudel et al., 2015). These responses are first mediated through stress systems that contribute to the redirection of blood flow to prioritize delivery to vital organs at the expense of skeletal muscle and other visceral tissue growth (Galan et al., 1999). Brain sparing activity in conjunction with impaired skeletal muscle growth results in an asymmetric growth pattern (Galan et al., 1999; Macko et al., 2013) and by term, fetal growth can be reduced by up to 50% compared to their uncompromised counterparts. Along with growth disparities, developmental adaptations contribute to a multitude of tissue specific metabolic dysfunction within the pancreas (Limesand et al., 2006; Leos et al., 2010), adipose tissue (Chen et al., 2010), skeletal muscle (Yates et al., 2016; Rozance et al., 2018; Cadaret et al., 2019a), liver (Thorn et al., 2009; Brown et al., 2015), heart, and brain (Poudel et al., 2015) of the fetus. Although these developmental adaptations occur to increase survivability *in utero*, they elicit life-long growth and metabolic changes that can impact favorable production traits and reduce efficiency in livestock.

MODELS OF DEVELOPMENTAL PROGRAMMING APPLICABLE TO LIVESTOCK PRODUCTION

Clinical cases of developmental programming can be studied in humans, but animal models have become increasingly useful to understand fetal pathophysiological and mechanistic changes throughout gestation (Anthony et al., 2003; Barry et al., 2006). The ovine model of IUGR is widely accepted as an ideal model (reviewed by Beede et al., 2019), due to similarities with human gestational milestones, as well as relatively comparable developmental stages to other ruminants such as cattle (Anthony et al., 2003). The tendency for singletons or twins, in addition to the average size of offspring, make sheep a more ideal model compared to the small litter-bearing species of rodents that are often used for human studies. Lastly, sheep tend to be more tolerable to surgical manipulation during gestation, with fetal size large enough to allow surgical catheterization to monitor maternofetal gas and nutrient transfer (Morrison, 2008). For these reasons, more literature exists about the effects of fetal programming in sheep, but these models have also been extended to cattle. Although the information provided by animal models is useful in improving perinatal morbidity and mortality rates in humans, in many cases it can also be applicable to livestock settings. With the help of ruminant models of developmental programming, producers can optimize nutrient intake in both critical pre and postnatal settings to improve growth for various food animals. The degree to which developmental programming occurs varies based on the model (Anthony et al., 2003), however, each animal model allows for

greater insight into mechanisms of developmental and postnatal growth and metabolic efficiency. In this section, we will cover ruminant models and, when not available, rodent models of developmental programming that mimic naturally occurring insults within production systems including heat stress, maternal inflammation, nutrient restriction, maternal obesity, and fetal exposure to glucocorticoids.

Heat Stress

Induction of fetal growth restriction through maternal exposure to high ambient temperatures has created a long-standing animal model for developmental programming. This model has been refined in the ovine, consistently producing placental insufficiency-induced IUGR (PI-IUGR) and entails placement of ewes into conditions ranging from 35 to 40°C with ∼35% relative humidity, for 50 consecutive days (Beede et al., 2019). Treatment begins around the 40th day of gestation to coincide with peak placental growth, ultimately causing placental stunting (Hay et al., 2016; Limesand et al., 2018). PI-IUGR has been established through many studies, implicating fetal hypoxia and hypoglycemia as the drivers of adaptive growth (Thureen et al., 1992; Limesand et al., 2018). As placental stunting occurs prior to exponential fetal growth, impacts are not observed until the third trimester when the placenta can no longer meet the demand of the growing fetus resulting in fetal malnutrition.

Sustained maternal hyperthermia from early to late gestation results in greater reduction of placental and fetal mass (up to 64 and 30–60% reduction, respectively) compared to exposure from mid to late gestation (Bell et al., 1989; Galan et al., 1999), substantially increasing perinatal death (Van Wettere et al., 2021). Developmental adaptations become a permanent change to the phenotype of the fetus when the insult is not removed in time, but it is possible for the fetus to experience compensatory growth or even fully restore placental function when the insult is removed before 55 days of gestation in sheep (Galan et al., 1999). Despite these variations, maternal heat stress has been associated with reduced birth weights, reduced survival rates prior to weaning, postnatal metabolic dysfunction, and a reduction in carcass merit in cattle and sheep (Yates et al., 2011; Monteiro et al., 2016; Limesand et al., 2018; Dahl et al., 2019). Catecholamines secreted as a response to hypoxia and hypoglycemia impair insulin secretion and responsiveness contributing to metabolic adaptations that result in increased adiposity and fat storage during early postnatal phases of compensatory growth (Limesand et al., 2006; Yates et al., 2011). Slowed myoblast proliferation leading to decreased fiber size (Yates et al., 2016), and reduced capacity for insulin stimulated glucose utilization (Limesand et al., 2007, 2018; Chen et al., 2010) contribute to altered muscle development and asymmetric growth patterns manifesting as poor body composition in animals after birth. There is also evidence of reduced placental transfer of amino acids (Regnault et al., 2013), along with decreased circulation of anabolic factors further suppressing cardiac and skeletal muscle growth (Bartelds et al., 2000). Additional organ weights such as thymus, spleen, heart, and liver have been shown to be reduced in newborn bull calves after gestational heat stress (Ahmed et al., 2021). Dairy cattle experiencing heat stress *in utero* can exhibit decreased body weight for up to 1 year of age, along with greater susceptibility to illness caused by comprised passive immunity (Tao et al., 2012; Monteiro et al., 2016; Davidson et al., 2021) putting animals at greater risk of death. However, perinatal heat abatement strategies have been shown to improve dairy calf growth and welfare and may serve as a strategy to prevent or mediate outcomes of *in utero* heat stress (Dado-Senn et al., 2020). Multiple studies have also demonstrated that late gestation heat stress impacts mammary development, which may contribute to persistent poor calf performance in future generations (Skibiel et al., 2018a,b; Ouellet et al., 2020).

Heat stress is known to impact maternal reproductive health and performance during gestation (recently reviewed by Alves et al., 2020; Van Wettere et al., 2021), but recent studies in dairy cattle indicate it may have lasting effects on adult offspring fertility as well. Indeed, animals whose dams were exposed to heat stress during gestation had longer days to first service, calving to conception interval, greater culling rate, and reduced Anti-Mullerian hormone (AMH) concentrations (Akbarinejad et al., 2017). A study in dairy cows found that heat stress did not appear to effect age of first insemination and parturition but did result in an increase in the number of services per pregnancy, increased age at pregnancy, and fewer calves survived to their first lactation (Monteiro et al., 2016). While there is growing research on the impacts of heat stress on pregnant dairy cows and their progeny fertility, data in grazing ruminants is missing and remains an area needing attention.

Maternal Inflammation

Maternofetal inflammatory responses are strongly associated with hypoxia induced by placental insufficiency from various causes (Bertucci et al., 2011). One such cause can be sustained maternal inflammation, like that seen with prolonged illness, which directly causes fetal inflammation and while not confirmed yet, likely placental insufficiency (Beede et al., 2019). Periods of infection, such as those seen with respiratory diseases that are common in livestock species, result in a febrile response and systemic inflammation that can last for multiple weeks (Gifford et al., 2012). Heat stress and lameness can also induce chronic systemic inflammation when not alleviated (Swanson et al., 2020). Much of the research around the influence of inflammation on animal performance is performed outside of gestational windows yet pregnant animals have increased susceptibility as their immune system is altered in early gestation to allow for establishment of pregnancy (Hansen, 2011). Thus, more data is needed to identify the prevalence of systemic inflammation during pregnancy in production settings. In an experimental setting we have implemented a model of maternofetal inflammation-induced IUGR (MI-IUGR) in the sheep and rat that involves the administration of the endotoxin lipopolysaccharide (LPS) to gestating animals, and found similar results to other models of IUGR (Cadaret et al., 2019a,b). Skeletal muscle is highly responsive to inflammatory regulation (Frost et al., 1997), and enhanced cytokine expression in ovine models of MI-IUGR impairs myoblast function and diminishes muscle fiber hypertrophy, contributing to decreased total body weight

in the near term fetus and postnatal lamb (Cadaret et al., 2019a; Posont et al., 2019). Along with dynamic changes in skeletal muscle growth, shifts in skeletal muscle glucose metabolism can be seen as part of the adaptive response to increased maternal inflammation, as fetal and postnatal MI-IUGR lambs demonstrate reduced glucose oxidation and impaired insulin regulation (Cadaret et al., 2019b; Posont et al., 2019). These responses to maternofetal inflammation persist postnatal and often result in asymmetric growth, impaired growth capacity, β-cell function, and metabolic capacity along with low birthweight pathologies in the sheep.

Since the MI-IUGR model is relatively new, factors outside of skeletal muscle growth and glucose metabolism have not been addressed in the literature. Hence, there is a lack of knowledge about the relationship between maternofetal inflammation and reproductive competency in progeny. While not in a ruminant species, a preliminary study in rats found that chronic maternal inflammation decreases the proportion of preantral follicles and AMH in offspring from LPS treated dams (Shalom-Paz et al., 2017). To our knowledge, no other studies exist in any species related to maternofetal inflammation, providing a gap in the literature around the role of inflammatory pathways in the programming of reproductive competency and efficiency.

Maternal Nutrient Restriction

Nutrient imbalance is an especially common precursor of maternal stress in animals. Rangelands of grazing livestock can have large fluctuations in quantity and quality of forage, leaving these animals predisposed to prolonged periods of undernutrition (Anderson, 1993; Bohnert and Stephenson, 2016). Models of maternal nutrient restriction have not consistently indicated placental stunting; although, the direct reduction in maternal nutrient status results in reduced placental uptake and decreased blood flow (Vonnahme, 2012). As such, fetal growth restriction may not always be evident, but adaptations to this insult can be seen at various gestational timepoints (Painter et al., 2005), providing greater insight to the tissue specific adaptive fetal mechanisms. Undernutrition during early gestation is more subdued compared to mid-late gestation, especially if animals are realimented by late gestation, and any growth deficits can likely be overcome by proper nutrition after birth (reviewed by Kenyon and Blair, 2014; Bell and Greenwood, 2016). Since it is considered relatively easy to implement this model, considerable research has focused on both the fetal and postnatal consequences of developmental programming due to maternal undernutrition. To mimic low forage quality, gestating animals will often be fed a diet consisting of ∼50–70% of their nutritional requirements (Vonnahme et al., 2003; Ford et al., 2007; Martin et al., 2007; Beede et al., 2019) for differing lengths of time, inducing a series of fetal developmental adaptations varying in severity based on the degree of malnutrition.

Multiple studies using maternal undernutrition have shown programmed growth and development of the fetus *in utero* and postnatal, along with alterations to normal placental development (Vonnahme et al., 2007; Funston et al., 2010; Vonnahme, 2012), sometimes paired with reduced placental weight (Heasman et al., 1999). When ewes were fed a diet composed of 50% National Research Council (1985) requirements from days 28 to 78 of gestation, fetal weight was reduced by ∼7.5% (Vonnahme et al., 2003). A similar study implemented the same diet restrictions and reported a decrease in birth weights, and significant catch-up growth with nutrient restricted (NR) lambs weighing more at 4 months of age and at slaughter (280 days) than control lambs (Ford et al., 2007). Compensatory weight gain may be attributed to increased plasma leptin concentrations that often favor fat deposition over muscle growth, as indicated by increased backfat thickness (Ford et al., 2007). Like other models, undernutrition is associated with hypoinsulinemia, hypoglycemia, and increased cortisol that promotes the development of glucose intolerance and insulin resistance (Ford et al., 2007; Cripps et al., 2008). Vulnerability of skeletal muscle to changes in nutrient availability additionally contributes to changes in body composition (Funston et al., 2010). Zhu et al. (2006) found damage to skeletal muscle development, evident by reductions in skeletal muscle mass, muscle fiber number, and Type IIa oxidative fibers. This coincided with reductions in GLUT 4 receptors in lambs slaughtered after 120 days of age, which indicates alterations to insulin sensitivity and glucose utilization in skeletal muscle (Zhu et al., 2006). Metabolic changes, reductions in loin muscle area, and increased fat mass (Lemley et al., 2012) of young sheep and cattle can persist throughout weaning and at slaughter compromising the weight and quality of carcasses (Larson et al., 2009). One model in dairy heifers, while not direct nutrient restriction, found that heifers born from dams lactating during gestation showed decreased milk production, survivability, and metabolic efficiency compared to heifers born to dams that were not lactating (Gonzalez-Recio et al., 2012) likely due to the competition of nutrients between the fetus and milk production.

Growth and metabolic adaptations occur concurrently to reproductive changes in NR offspring (reviewed by Chavatte-Palmer et al., 2014). Early gestational nutrient restriction in cattle followed by protein supplementation reduced healthy antral follicle count, prepubertal follicle size, and primordial follicle density at nearly 2 years of age (Sullivan et al., 2009). Similarly, early gestational nutrient restriction in cattle results in reductions in AMH concentrations along with diminished ovarian reserve (Mossa et al., 2013). In ewes, maternal nutrient restriction prior to or during folliculogenesis results in delayed ovarian reserve development (Rae et al., 2001). Other studies in ewes have exhibited impaired pituitary function in nutrient restricted offspring, influencing endocrine regulation of cellular proliferation, and reproductive function (Kotsampasi et al., 2009b; Long et al., 2021). Additionally, nutrient restriction in the first 95 days of pregnancy in ewes was shown to reduce ovulation rate in female progeny, independent of growth restriction or endocrine dysregulation (Rae et al., 2002) impacting fertility of adult female offspring born from nutrient restricted dams.

In male ruminant offspring, gestational nutrient restriction results in declines in both the number of Sertoli cells and the diameter of seminiferous tubules without changes in hypothalamic-pituitary-gonadal (HPG) regulation or testis weight (Kotsampasi et al., 2009a; Martín et al., 2012). Fortunately, age of puberty in both sexes appears largely uninfluenced by

maternal undernutrition (Rae et al., 2002; Sullivan et al., 2009). However, as gonadal development and growth appears to be vulnerable to gestational nutrient restriction, more research is needed to evaluate if these transient changes impact lifelong reproduction, as reproductive efficiency is a major driver of ranch productivity and profitability.

Maternal Overnutrition

Another popular model for inducing adaptive fetal programming involves the over feeding of adolescent ewes. When over nourished, the adolescent body will preferentially allocate nutrients toward maternal growth, compromising fetal growth and development (Anthony et al., 2003). To achieve maternal obesity, many models supply diets ranging anywhere from 140 to 200% of the NRC requirements at varying stages of pregnancy (Swanson et al., 2008; Tong et al., 2009; Carr et al., 2012). One of the major limitations of this model is maternal age, as mature animals vary in outcomes between fetal growth restriction or overgrowth, making growth impacts difficult to determine (Tong et al., 2009). Fortunately, the model still provides insight into fetal programming caused by maternal obesity which can be seen in ruminant animals.

Similar to the previous models of fetal programming, the severity of insult varies based on the timing and duration of the insult. Wallace et al. (1999) discovered that early dietary interventions provided opportunity to recover fetal growth, but those insults persisting through later gestational stages resulted in permanent adaptations. It was also determined that reductions of maternal dietary intake from high to moderate throughout mid-gestation enhanced fetal growth, while increased dietary intake at the same time leads to reductions in both placental and fetal growth (Wallace et al., 1999). Continued overnourishment prompts fetal hypoxia and hypoglycemia due to impaired uterine arterial and umbilical venous blood flow (Wallace et al., 1999, 2002), reducing placental and fetal mass by ∼45% (Wallace et al., 2002; Wallace, 2019). By mid-gestation, growth restricted fetuses also experience low insulin and IGF-1 concentrations and high lactate concentrations (Wallace et al., 2003), along with a greater fat deposition (Matsuzaki et al., 2004). On average, over nourished ewes with reduced placental mass experience a shorter gestational length and are at greater risk for abortion or stillbirth (Wallace, 2019). Fetuses that survive gestation and parturition after maternal overnourishment exhibit asymmetric growth, along with an increase in weight of major endocrine organs such as the pancreas and pituitary gland (Wallace, 2019). Offspring with moderately reduced birthweight often experience rapid catch-up growth, reaching average control size by weaning (Wallace et al., 2010, 2012), while those with severely reduced birth weights remain smaller through mid-adulthood (Wallace et al., 2018). Maternal overnutrition, while seemingly counterintuitive, decreases the quality and quantity of colostrum, specifically immunoglobulin G (IgG), causing a lack of passive immunity and further contributing to decreased survivability (Swanson et al., 2008). Along with changes to postnatal body composition, these offspring tend to have altered metabolic phenotypes including altered glucose metabolism and glucose intolerance (Wallace et al., 2012, 2014) throughout all life stages leading to an obese phenotype, particularly in females (Wallace et al., 2018). The obese phenotypes, as would be expected, result in greater adiposity and less muscling leading to decreased carcass merit.

Subsequent female offspring fertility is affected more by maternal obesity than males, evidenced by diminished ovarian reserve and development, with major reductions in primordial follicle number in fetuses from obese ewes (Da Silva et al., 2002, 2003). Reduced ovarian reserve may be attributed to disruption of meiotic germ cell activity along with altered estrogen and inhibin feedback from the fetal ovaries and placenta (Da Silva et al., 2002). Fortunately, female sheep reach puberty at similar ages to controls and exhibit average estrous cyclicity during the first breeding season (Da Silva et al., 2001). Contrarily, male reproduction is un-influenced when determined by number of Sertoli cells, seminiferous tubules, or pituitary gonadotroph expression in offspring of over nourished dams compared to their control counterparts (Da Silva et al., 2003). However, male lambs from overnourished dams were slower growing, had delayed age of puberty, smaller testicular volume, and reduced testosterone, which may influence sperm quality and quantity and reduce fertility (Da Silva et al., 2001; Wallace, 2019). Overall, this model has shown that excess maternal nutrition influences male and female reproductive capacity in some regard, and that these effects are evident with and without growth restriction.

Excess Glucocorticoids

As part of a the stress response to nutrient challenge, circulating cortisol concentrations increase in the dam and fetus (Phillips et al., 1998; Roussel et al., 2004). Increased cortisol concentrations are believed to contribute to rapid maturation of organ systems, which makes late-gestation administration of synthetic glucocorticoids a common clinical practice to improve neonatal outcomes in instances of pre-term labor in humans (Seckl, 2001; Kapoor et al., 2008). However, recent studies have begun to indicate a correlation between excessive increases in maternofetal cortisol concentrations and a neonate phenotype similar to previous models of adaptive fetal programming (Seckl, 2001; Long et al., 2012), such as reduced birthweight, aberrant metabolism, and poor body composition.

Studies administering synthetic glucocorticoids in the early third trimester have revealed associations between fetal exposure to glucocorticoids and reduced birth weight, metabolic dysfunction, and endocrine alterations (Long et al., 2012, 2013a,b). Under normal circumstances, passage of maternal glucocorticoids to the fetus is minimal due to the presence of the placental enzyme 11β- hydroxysteroid dehydrogenase (11β-HSD) type 2, catalyzing the conversion of maternal cortisol to ketone products, protecting the fetus from excess glucocorticoid exposure (Seckl et al., 1995; Kapoor et al., 2008). Synthetic glucocorticoids however cannot be metabolized by 11β-HSD 2, consequently allowing placental transfer and increasing fetal glucocorticoid exposure (Kapoor et al., 2008). Along with a significant decrease in birthweight, ovine models have indicated alterations in function of the fetal and postnatal hypothalamic-pituitary-adrenal (HPA) axis in response to elevated glucocorticoids (Sloboda et al.,

2002, 2007; Long et al., 2013a). Fetal sheep with repeated exposure to glucocorticoids throughout gestation have shown increased circulating adrenocorticotropic hormone (ACTH; Long et al., 2013a) and cortisol concentrations through increased pituitary glucocorticoid receptors (Sloboda et al., 2000). Upon further investigation, it was observed that offspring exposed to excess glucocorticoids through maternal injection exhibit greater adrenal sensitivity in early life (until about 1 year of age) (Sloboda et al., 2007), but this decreases with age. Glucocorticoids also program hormones that regulate appetite and glucose metabolism in offspring. Lambs from ewes administered dexamethasone during the last third of gestation were absent of a postnatal leptin surge, possibly due to antagonistic elevated cortisol observed concurrently (Long et al., 2013b). This was paired with increased appetite that resulted in weight gain in favor of adipose deposition during an *ad libitum* feeding trial (Long et al., 2013b). Additionally, these animals were hyperglycemic and exhibited β-cell dysfunction when put through a glucose tolerance test (Long et al., 2012, 2013a) which is a finding in other models of developmental programming as well.

Glucocorticoids have the ability to act upon various tissue types including reproductive tissue *via* glucocorticoid receptors (Zambrano et al., 2014). Similar to the endocrine changes seen in the HPA axis, it is believed that glucocorticoids can also program changes to hormonal function of the HPG axis; however, most of these studies have been performed in rodents (Zambrano et al., 2014). Ovine studies have shown alterations to morphologic development of testes after prenatal glucocorticoid exposure (Pedrana et al., 2008), contributing to possible programming of reproductive development. Studies in female rats exposed to glucocorticoids prenatal have shown a decrease in follicle number (Ristic et al., 2008), while studies of human ovaries exposed to glucocorticoids exhibit a decrease in number of germ cells along with increased rates of apoptosis (Poulain et al., 2012). As increased glucocorticoids can be endogenous from maternofetal stress, induced exogenously as a treatment for impending preterm birth, or a method of labor induction, these data encourage further investigation of the long-term impacts and potential methods to mediate them.

EVIDENCE OF INTERGENERATIONAL PROGRAMING IN RUMINANT LIVESTOCK

There is compelling human and rodent data to suggest the outcomes of an adverse *in utero* environment, persist into subsequent generations in what is described as intergenerational or transgenerational programming (reviewed by Aiken and Ozanne, 2014). Intergenerational programming refers to conditions in one generation that impact the development, growth, metabolism, and health in future generations, without secondary insult. It is important to note that since an adverse *in utero* environment impacts a fetus and the developing germ cells within the fetus, alterations must be sustained into the F3 generation and beyond to be considered transgenerational (Khatib, 2021). While evidence of intergenerational programming is available, the mechanism that allows transmission is poorly understood. Current hypotheses and areas of investigation include epigenetic mechanisms passed through the germline, programmed maternal physiological mechanisms, and persistent environmental influences; however, the answer is likely a combination of multiple mechanisms (**Figure 1**; Drake and Walker, 2004). Most of the transgenerational data has come from observational human studies or rodents, but, in recent years some intergenerational studies have extended to livestock species to characterize the phenotypic changes that occur between generations. Studies investigating generational impacts of developmental programming in ruminant livestock are limited (**Table 1**), in this section we recapitulate current findings that hold relevance to animal agriculture and may serve as areas to target for management practices that mediate multigenerational programming.

Environmental perturbations can change plane of nutrition rapidly for grazing livestock, making nutrient availability perhaps the most common stress livestock can encounter. Studies completed at the University of Wyoming using groups of sheep from genetically similar backgrounds but vastly different production systems (well-nourished university housed sheep vs. nutrient restricted "nomadic" sheep) provide perhaps the only evidence of transgenerational programming in ruminants over ∼ 5 generations (Vonnahme et al., 2006). When both groups were subjected to a 50% nutrient restriction, nomadic ewes outperformed university ewes with maintenance of ideal BCS for a longer period of time, heavier fetuses, and no difference between fetal measurements. The ability of nomadic ewes to maintain normal fetal growth is credited to placentome conversion that maintains fetal nutrient delivery, suggesting adaptive programming to nutrient restriction that has been carried over generations (Vonnahme et al., 2006; Jobgen et al., 2008). Further investigation is needed to understand how many generations it takes for these adaptations to occur as nutrient restriction in the first generation generally exhibits poor fetal outcomes, as described in previous sections of this review. Indeed, other studies investigating impacts of granddam nutrition in early gestation found varying results in daughters and granddaughters lactation performance (Van Der Linden et al., 2009), birth weight (Kenyon et al., 2014), weaning weights (Paten et al., 2013), organ morphometrics (Martín et al., 2012), and reproductive performance (Blair et al., 2010) depending on timing and duration of insult. It is worth noting that in these studies ewes were nutrient restricted in early pregnancy then realimented for the remainder of gestation. Further research is needed to understand the impacts of restriction in mid-late gestation across generations.

Intergenerational programming has been observed in models of overnourished sheep as well, extending to the F2 generations. Sheep fed 150% of NRC requirements during gestation had daughters and granddaughters with elevated cortisol concentrations, hyperglycemia, insulin resistance, and increased adiposity even when provided a normal diet (Shasa et al., 2015). Follow-up studies found these effects appear to be sex specific as male lambs from overfed granddams had greater body mass compared to female lambs or controls.

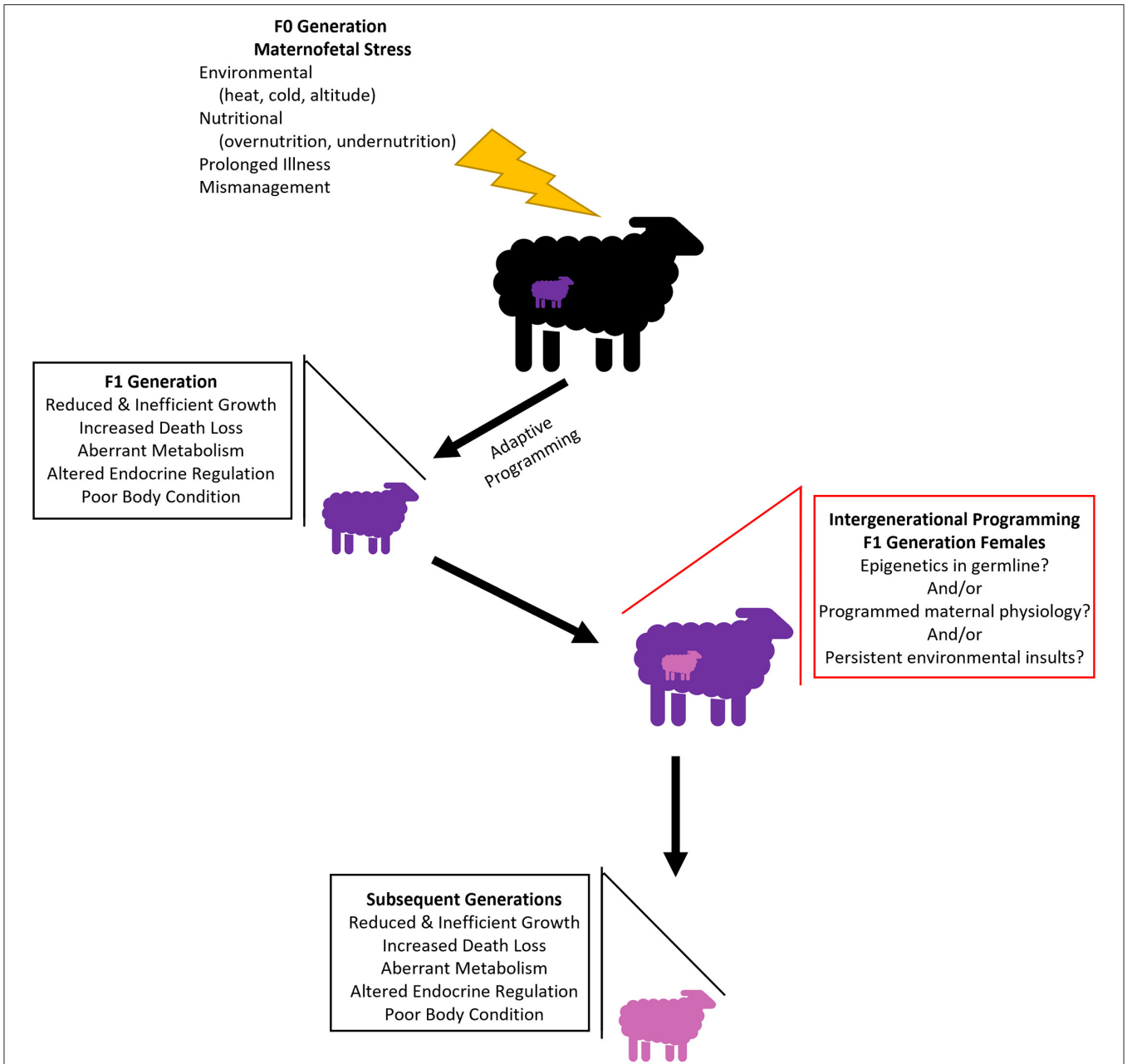

FIGURE 1 | Current proposed hypotheses of the cascade of intergenerational programming in ruminant livestock. Initial maternofetal stress results in developmental programming in the first generation. While mechanisms are not yet clear, similar phenotypes are propagated into subsequent generations.

Furthermore, females from these overfed granddams had dysregulated insulin:glucose dynamics compared to male lambs or controls (Pankey et al., 2017) and these effects may carry into the F3 generation (Pankey et al., 2021). Alternatively, Van Der Linden et al. (2010) found that heavier dams increased lamb birth weight but did not impact female offspring reproductive performance. However, granddams fed to maintenance had granddaughters with heavier birth and weaning weights compared to granddams fed *ad libitum* regardless of dam bodyweight.

Pregnant ewes administered synthetic glucocorticoids toward the end of gestation have shown similar intergenerational outcomes. Lambs from treated ewes had reduced birthweight, were structurally smaller than their control counterparts, and had altered glucose utilization and HPA axis responsiveness (Long et al., 2012, 2013a). These findings carried over into the F2 progeny showing tissue specific programming in an untreated population. Focusing on the F2 generation, Long et al. (2013b) found that F2 lambs did not experience the neonatal leptin peak and had increased cortisol concentrations which were paired with

TABLE 1 | Studies showing intergenerational effects of maternofetal stress in ruminant livestock.

References	Species	F0 maternal insult	F1 generation	F2 generation	F3 generation
Long et al. (2012)	Ovine	GC	↓ birthweight, morphometrics, β-cell function, postnatal weight ↑ fasting glucose	↓ birthweight, morphometrics, β-cell function ↑ fasting glucose	
Long et al. (2013a)	Ovine	GC	↑ basal cortisol, HPA hyperresponsiveness	↑ basal cortisol, ACTH, HPA hyperresponsiveness	
Long et al. (2013b)	Ovine	GC	↓ birthweight, morphometrics, growth rates	↓ birthweight, morphometrics, growth rates, leptin ↑ appetite, weight gain, adiposity, leptin, glucose, cortisol	
Jobgen et al. (2008)	Ovine	NR	↓ fetal growth, maternal & fetal plasma amino acids	↑ fetal to maternal concentrations of polyamines, ND fetal amino acids	
Shasa et al. (2015)	Ovine	ON	Absent postnatal leptin surge ↑ postnatal blood cortisol, insulin, glucose	Absent postnatal leptin surge ↑ blood cortisol, glucose, insulin, percent body fat at birth.	
Pankey et al. (2017)	Ovine	ON	Absent postnatal leptin surge ↑ abdominal adiposity, cortisol, leptin ↓ β-cell function Insulin/glucose dysregulation	Rapid weight gain ↑ insulin resistance ↓ β-cell function Insulin/glucose dysregulation	
Pankey et al. (2021)	Ovine	ON	↑ cortisol, adiposity Insulin/glucose dysregulation Hyperphagia	↑ cortisol, adiposity, weight gain, insulin resistance Insulin/glucose dysregulation Hyperphagia	ND in body composition.
Van Der Linden et al. (2009)	Ovine	ON	↓ mammary gland weight, growth rates, lamb weight until weaning, milk yield, lactose percentage, accumulated CP yields	↓ growth rates to weaning	
Van Der Linden et al. (2010)	Ovine	ON	ND in live weight, BCS, breeding percentage, number of fetuses	↓ birthweight, weaning weight	
Blair et al. (2010)	Ovine	ON	↑ mammary ductal size, secretory cell area, IGF-1 receptors, accumulated fat yield, milk net energy	↓ birthweight, proportions of ewes reaching puberty	
Paten et al. (2013)	Ovine	ON & NR	↓ BCS in late gestation for ewes born from NR dams. ↓ milk yield, milk fat, and milk net in ewes born from NR & ON ewes.	↓ body weight until weaning in lambs born from early gestational ON ↑ body weight until weaning in late gestation ON	
Kenyon et al. (2014)	Ovine	ON & NR	↓ gestational weight, backfat thickness, BCS in lambs from NR. ↓ gestational BCS in lambs from ON	ND in lamb live weight between ON & NR	
Laporta et al. (2020)	Dairy Cattle	HS	↓ survivability, milk yield up to three lactations.	↓ milk yield through first lactation.	

ACTH, adrenocorticotropic hormone; BCS, body condition score; CP, crude protein; GC, glucocorticoid administration; HPA, hypothalamic pituitary axis; HS, heat stress; IGF-1, insulin-like growth factor 1; ND, no difference; NR, nutrient restrictions; ON, over nutrition. ↑, increased; ↓, decreased.

increased appetite, body weight gain in favor of fat deposition, and impaired insulin response resulting from glucocorticoid treatment of their granddams.

The dairy industry has seen evidence of intergenerational programming in response to heat stress (Ouellet et al., 2021). Indeed, in a retrospective study, cows exposed to heat stress in late gestation had daughters that left the herd earlier, had reduced initial milk yield in their first three lactations, and had differences in milk components. Effects were also seen in the granddaughters of these cows as they displayed delayed age at first AI, reduced initial milk yield in their first three lactations, and differences in components of the milk (Laporta et al., 2020). Studies in Israel also found that heat stress during mid-gestation for F0 cows had negative effects out to the F3 generation for traits associated with production and calving (Weller et al., 2021). It is believed that this was possible due to preservation of epigenetic modification during the F1 progeny development (Klosin and Lehner, 2016; Weller et al., 2021), however, further research is warranted.

CONCLUSION

Animal models of adaptive fetal programming have become increasingly useful to understand the pathophysiologic and mechanistic changes that result in adaptive phenotypes. The bulk of this research within livestock focuses largely on the fetal adaptations, while the postnatal life of these

offspring remains less understood. Future research to improve the wellbeing and productivity of food animals requires in depth evaluation of the long-term effects on production agriculture, including evaluation of growth patterns, efficiency, longevity, reproductive capabilities, and carcass traits. While maternal performance is a major driver of herd productivity and profitability there seems to be a general lack of information, outside direct maternal nutrition, on programming influences of reproductive efficiency in the first and subsequent generations. Current data begins to illustrate intergenerational programming events in ruminant livestock stemming from various maternal stressors. As these studies are limited, more research is necessary to improve understanding of how various environments and timepoints impact lifelong performance. Further, larger studies that provide knowledge better characterizing the relevance and extent of the impact are warranted, including following animals into the F3 generation and beyond. Investigations into current hypotheses of heritable phenotypes that increase understanding of environmental, epigenetic or programmed changes in subsequent generations are needed and may inform production practices. Development of expected outcomes based on environmental interactions could aid in identification of compromised animals faster and better interventional management.

AUTHOR CONTRIBUTIONS

AV and CC contributed to drafting and revision of manuscript. All authors contributed to the article and approved the submitted version.

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