ADSA Foundation Scholar Award: New frontiers in calf and heifer nutrition—From conception to puberty

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ABSTRACT

Dairy calf nutrition is traditionally one of the most overlooked aspects of dairy management, despite its large effect on the efficiency and profitability of dairy operations. Unfortunately, among all animals on the dairy farm, calves suffer from the highest rates of morbidity and mortality. These challenges have catalyzed calf nutrition research over the past decade to mitigate high incidences of disease and death, and improve animal health, growth, welfare, and industry sustainability. However, major knowledge gaps remain in several crucial stages of development. The purpose of this review is to summarize the key concepts of nutritional physiology and programming from conception to puberty and their subsequent effects on development of the calf, and ultimately, future performance. During fetal development, developmental plasticity is highest. At this time, maternal energy and protein consumption can influence fetal development, likely playing a critical role in calf and heifer development and, importantly, future production. After birth, the calf's first meal of colostrum is crucial for the transfer of immunoglobulin to support calf health and survival. However, colostrum also contains numerous bioactive proteins, lipids, and carbohydrates that may play key roles in calf growth and health. Extending the delivery of these bioactive compounds to the calf through a gradual transition from colostrum to milk (i.e., extended colostrum or transition milk feeding) may confer benefits in the first days and weeks of life to prepare the calf for the preweaning period. Similarly, optimal nutrition during the preweaning period is vital. Preweaning calves are highly susceptible to health challenges, and improved calf growth and health can positively influence future milk production. Throughout the world, the majority of dairy calves rely on milk replacer to supply adequate

nutrition. Recent research has started to re-evaluate traditional formulations of milk replacers, which can differ significantly in composition compared with whole milk. Transitioning from a milk-based diet to solid feed is critical in the development of mature ruminants. Delaying weaning age and providing long and gradual step-down protocols have become common to avoid production and health challenges. Yet, determining how to appropriately balance the amount of energy and protein supplied in both liquid and solid feeds based on preweaning milk allowances, and further acknowledging their interactions, shows great promise in improving growth and health during weaning. After weaning and during the onset of puberty, heifers are traditionally offered high-forage diets. However, recent work suggests that an early switch to a high-forage diet will depress intake and development during the time when solid feed efficiency is greatest. It has become increasingly clear that there are great opportunities to advance our knowledge of calf nutrition; yet, a more concentrated and rigorous approach to research that encompasses the long-term consequences of nutritional regimens at each stage of life is required to ensure the sustainability and efficiency of the global dairy industry.

Key words: calf, heifer, nutrition, development

INTRODUCTION

The overall goal of rearing calves and replacement heifers is to raise healthy and nutritionally efficient animals in a humane and cost-effective manner. Most rearing strategies aim to reduce the age at first calving to lessen nonproductive days, while ensuring that heifers achieve sufficient frame size and organ development without compromising milk production (Heinrichs et al., 2017; Van Amburgh et al., 2019; Erickson et al., 2020). Over the past 2 decades, knowledge of developmental and nutritional programming of young livestock animals has advanced (Soberon et al., 2012; Bartol et al., 2013; Gelsinger et al., 2016). This research suggests that several key windows of developmental program-

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ming (fetal, neonatal, preweaning, weaning, pre- and postpubertal) exist, in which nutritional management in utero to first calving may contribute to the overall development of the calf, and ultimately, to improved future milk production (Berry et al., 2008; Heinrichs et al., 2017; Kertz et al., 2017). Showcasing the positive, long-term outcomes of improving early-life growth and health has stimulated greater interest in calf research, with the amount of research dedicated to heifer nutritional management doubling over the past decade (Heinrichs et al., 2017). Despite growing interest, 10 to 15% of heifers born do not reach first calving (De Vries and Marcondes, 2020), demonstrating that there is still significant room to improve heifer management strategies. These strategies can be largely improved by optimizing nutritional management, which has the potential to benefit the dairy industry via improved production, efficiency, health, and animal welfare.

Developmental plasticity is defined as the ability for the same genotype to produce different phenotypes through epigenetic regulation (Hochberg et al., 2011). In animals, developmental plasticity begins, and is most dynamic, at conception, which suggests that the prenatal and early postnatal periods have the greatest potential for nutritionally programming the calf (Fig-

ure 1; Bartol et al., 2013). Despite this critical window, this field has only recently gained research interest, as emerging evidence suggests that milk production potential can be initially programmed in utero, signaled by nutritional or environmental changes experienced by the dam (Dahl et al., 2019; Carvalho et al., 2020; Van Eetvelde and Opsomer, 2020). Postnatal, developmental programming may be influenced by early-life nutritional strategies, including management of colostrum and preweaning nutrient intake. During early life, it is well known that colostrum and milk intake play key roles in nutritional programming and can have subsequent effects on growth (Rauprich et al., 2000; Moallem et al., 2010), gut development (Hammon and Blum, 2002; Fischer et al., 2019) and future milk production (Faber et al., 2005; Soberon et al., 2012).

The preweaning and weaning periods have been the most studied (Figure 1) but remain among the most challenging stages of a calf's life, as reflected by high morbidity and mortality rates (USDA, 2016; Urie et al., 2018b). Calves are highly susceptible to disease during this period due to a combination of factors, including failed passive transfer of immunity (Shivley et al., 2018; Renaud et al., 2020), social stress, and environmental and housing conditions (Wilcox et al., 2013; Roland

Figure 1. Several key windows of developmental programming (embryo, fetus, neonatal, preweaning, weaning, pre- and postpubertal) exist throughout the first years of a heifer's life. As the calf ages, developmental plasticity—the degree by which environmental or nutritional conditions influence heifer development and phenotype—gradually decreases. During each developmental window, varying levels of maternal (green) and postnatal (blue) effects influence the heifer phenotype. These maternal and postnatal effects largely consist of dam nutrition during the embryonic and fetal periods and heifer nutrition from the neonatal to pubertal stage. Fundamental knowledge gaps related to nutritional management in utero to puberty that may contribute to the overall development of the calf and future productivity are described in text boxes below each developmental window.

et al., 2016). An estimated 5% of US dairy calves die during the preweaning period, and 33.8% experience a health disorder before weaning (Urie et al., 2018b). Digestive disorders remain the most common cause of morbidity and mortality for dairy calves, accounting for over half of reported illnesses and one-third of deaths (Urie et al., 2018b; Winder et al., 2018). Many health disorders, including diarrhea, experienced by calves during the preweaning and weaning periods can often be prevented or mitigated through well-developed nutritional management programs (Ollivett et al., 2012; Ballou, 2012). Additionally, optimizing nutritional strategies during the preweaning period can have significant economic benefits, as they not only directly affect mortality rate, disease susceptibility, and growth rate during the preweaning period, but also milk production later in life (Soberon et al., 2012; Soberon and Van Amburgh, 2013; Gelsinger et al., 2016).

There is a plethora of research investigating optimal solid feed programs for young calves and calves during weaning (Figure 1). Solid feed plays an important role in nutritional programming, as improved solid feed intake contributes to increased preweaning ADG, which positively influences first-lactation milk production (Soberon et al., 2012; Gelsinger et al., 2016). Moreover, research conducted during the prepubertal-to-first-calving period has focused on nutritional management that ensures adequate growth and development (Heinrichs et al., 2017; Van Amburgh et al., 2019; Erickson et al., 2020). There is currently a lack of research pertaining to nutritional management from the postpubertal stage to first calving and its effect on efficiency and productivity during lactation. Therefore, this narrative review will highlight some of the key nutritional contributors that influence heifer calf development at different life stages. These include nutritional physiology during the in utero, neonatal, preweaning, weaning, and prepubertal and pubertal stages of life, with key knowledge gaps highlighted and discussed for each life stage.

PRENATAL DEVELOPMENT AND NUTRITION

Prenatal programming is the process by which the embryo or fetus adapts to changes in the uterine environment reflecting alterations in the maternal environment (Reynolds et al., 2019). Phenotypic changes can be mediated by epigenetic mechanisms, such as differential gene expression without changes in the genetic code (Reynolds et al., 2019), direct effects on organ or tissue development in utero (Du et al., 2010), or a combination of both. These differences can be observed as early as the neonatal period (Alharthi et al., 2019; Haisan et al., 2019) or may appear later in life during lactation (González-Recio et al., 2012; Van Eetvelde et

al., 2017; Carvalho et al., 2020). Factors that program prenatal development in dairy calves include maternal age, malnutrition, metabolic and oxidative disturbance, heat stress, dry period length, and photoperiod (Van Eetvelde and Opsomer, 2017, 2020; Abuelo, 2020). The gestational onset, duration of time, and degree of severity of the prenatal programmer determine the signal strength to the fetus and the resulting phenotypic changes. Ultimately, in-depth knowledge of bovine fetal development and nutrient requirements is needed to understand how adverse programming effects can be prevented and to ensure potential benefits from epigenetic changes.

Gestational Nutrient Intake and Fetal Requirements

The NRC (2001) model estimates energy and protein requirements for gestating dairy cattle based on serial slaughter studies from 190 to 270 d postconception (House and Bell, 1993; Bell et al., 1995). Using the equations derived from these studies and considering that most fetal growth occurs between mid to late gestation, most nutrient requirements are presumed to be zero for the fetus up to 190 d postconception (NRC, 2001). Additionally, some mineral and vitamin requirements (sulfur, cobalt, iodine, selenium, and vitamin D) are not assumed to increase during gestation and, thus, are not factored within the model (NRC, 2001). Metabolizable energy and MP requirements after 190 d postconception are empirically modeled and corrected by their respective efficiencies of use (0.14 and 0.33; Ferrell et al., 1976; Bell, 1995) for gestation. Though estimates obtained using this approach are reasonably close to observed values during late gestation (Bell, 1995), there are some limitations to this method.

Predominantly, gestational nutrient requirements before 190 d postconception should not be disregarded. Sguizzato et al. (2020) determined that the energy requirement for pregnancy was different from zero at 70 d postconception and onwards in Holstein $\times$ Gyr dams. Slightly elevated maternal glucose concentrations (+13%) obtained through exogenous glucose infusion reduce conceptus length, width, and area 7 d after embryo transfer (Leane et al., 2018), demonstrating that the gravid uterus has a high sensitivity to fluctuating metabolites during early gestation. As peak milk production typically coincides with breeding and conception, homeorhetic nutrient partitioning toward lactation will alter the supply of metabolites available to the developing fetus and potentially program fetal development and postnatal insulin sensitivity (Kamal et al., 2014; 2015). Maternal metabolic health challenges can also program lactation characteristics in female progeny (Carvalho et al., 2020). Early maternal

malnutrition can alter fetal development (Duarte et al., 2013; Rotta et al., 2015; Gionbelli et al., 2018), although in utero compensatory growth during the later stages of gestation is possible (Pillai et al., 2017; Copping et al., 2020). The divergent in utero growth could have consequences for future progeny development without alterations in gross fetal development being apparent at birth.

Another concern is that framing fetal nutrient requirements in the context of maternal ME or MP requirements during gestation (NRC, 2001) simplifies which substrates are needed by the fetus for proper development. Glucose, lactate, and AA are the primary fetal oxidative substrates (Bauman and Currie, 1980; Bell, 1995); however, it is unknown how shifting maternal ME supply or source at different stages of gestation influences the availability of energetic substrates for oxidation or energy deposition in fetal tissue. Haisan et al. (2019) found that increasing dry period dietary starch content from 14.0 to 26.1% DM increased insulin area under the curve and maximum insulin concentration during an intravenous glucose tolerance test in neonatal calves. It is unclear whether total dietary energy content or the form of dietary energy supplied programmed neonatal and preweaning metabolic responses in this study; however, late-gestation maternal insulin resistance is correlated with metabolic traits in preweaned dairy calves (Kawashima et al., 2016; Hasegawa et al., 2019). Mediating the degree of insulin resistance experienced during late gestation might improve metabolic responses in preweaning calves, although it is still unclear how differing dietary energy content or source during early or mid-gestation would influence fetal development and postnatal metabolism.

The current NRC (2001) model reasonably predicts the MP requirement for conceptus development during late gestation (Bell, 1995); however, the model likely underestimates late-gestation MP requirements because it does not consider the MP required for mam-mogenesis (~120 g of MP/d; Bell et al., 2000), consequently causing a late gestation MP deficit. A recent meta-analysis validated this concept for primiparous heifers, demonstrating linearly improved production responses when heifers were fed up to 1,100 g of MP/d during late gestation (Husnain and Santos, 2019). More conservative responses were reported with multiparous cattle (Husnain and Santos, 2019), suggesting that MP requirements may be adequately modeled for late-gestation multiparous cows. However, it is crucial to acknowledge that this meta-analysis focused on cow production parameters without evaluating the influence of maternal MP supply on calf performance. In beef cattle, protein restrictions reduced plasma glucose and leptin and increased cortisol concentrations of calves

at birth (LeMaster et al., 2017), demonstrating that maternal protein deficits can affect offspring during the neonatal period. To our knowledge, the influence of prepartum MP under- or oversupply on the development of dairy calves has not been evaluated. Although MP-focused feeding does improve predictions regarding the adequacy of protein supply compared with CP-focused feeding, cattle still require the constituents of MP (i.e., metabolizable AA) for optimal performance (Lean et al., 2018; Nichols et al., 2019). Preliminary evidence suggests that late-gestation rumen-protected methionine supplementation has profound effects on placental metabolism and calf development when diets already oversupply MP (Alharthi et al., 2018, 2019; Batistel et al., 2018, 2019; Elolimy et al., 2019). Although these studies strongly implicate methionine as a limiting AA during late gestation, methionine supplementation caused imbalanced MP supply between treatments and increased DMI by 1.2 kg/d (Batistel et al., 2017); therefore, responses are confounded by both MP and nutrient intake.

Future Directions

Fetal development is complex and dynamic throughout all stages of gestation, and phenotypic responses in dairy calves will depend on the timing, duration and severity of the prenatal programmer. As the current NRC (2001) model does not consider the maternal requirements for gestation before 190 d, future models should account for the additional requirements for pregnancy before 190 d of gestation to ensure that nutrient supply optimizes fetal development. Dairy cows experience a negative energy balance in early pregnancy and are susceptible to overconditioning in late gestation, which may influence the growing fetus. Further research is needed to understand how maternal energy or protein supplies and sources modulate the availability of substrates for fetal metabolism. Additionally, the adequacy of protein supply and the role of specific metabolizable AA on the efficiency of protein utilization for gestation requires further evaluation. An improved understanding of substrate supply and utilization by the developing fetus will enable us to predict adverse or positive developmental programming outcomes in dairy calves.

NEONATAL PERIOD

After birth, neonatal calves require diligent care and management as their undeveloped immune system causes an inherent susceptibility to environmental pathogens. They depend on the timely consumption of colostrum to provide humoral immunity until their adaptive immune system becomes fully developed and

active (Weaver et al., 2000). Calves establish humoral immunity via colostrum by absorbing intact and functional colostral immunoglobulins, known as the transfer of passive immunity (**TPI**; Dunn et al., 2017). Improper colostrum feeding can compromise the calf's capacity to absorb adequate quantities of immunoglobulins, leading to an increased incidence of morbidity. Twelve and 24% of dairy calves in the United States (Shivley et al., 2018) and Canada (Renaud et al., 2020), respectively, suffer from failed TPI based on the traditional dichotomous standard of 10 mg of IgG/mL in serum (Quigley, 2004) or a serum total protein value ≤ 5.2 g/dL at 24 h of age (Buczinski et al., 2018). However, new serum IgG thresholds (poor: ≤ 10 g of IgG/L; fair: >10 g of IgG/L; good: >18 g of IgG/L; excellent: >25 g of IgG/L) have been established and are currently being recommended to promote calf health and survival (Lombard et al., 2020). Consequently, there will be a push for dairy producers to improve colostrum management to ensure neonatal calves achieve and surpass "good" serum IgG thresholds.

In terms of TPI, the components of a successful colostrum management program—quality, quantity, timeliness of colostrum feeding, low bacterial contamination, and colostrum source—have recently been reviewed in depth (Godden et al., 2019; Fischer-Tlustos et al., 2021). Thus, this section will largely focus on prepartum management strategies affecting colostrum composition, as well as the beneficial effects that colostrum may have on calf development through its myriad of bioactive components.

Cow, External, Nutritional, and Environmental Factors Affecting Colostrum Composition

Colostrum composition and quality, specifically IgG concentration, can vary greatly among cows and between farms (Morrill et al., 2012; Conneely et al., 2013). In general, colostrum composition can be affected by parity number, dry period length, colostrum volume, breed of the dam (Weaver et al., 2000), vaccination protocols (Dunn et al., 2017), disease exposure, diet (Tsioulpas et al., 2007; Mann et al., 2016), animal variation (Parish et al., 1950), onset of colostrogenesis (Baumrucker and Bruckmaier, 2014), individual farm variation (Guliksen et al., 2008), and endocrine regulation (Guy et al., 1994). Dry period length and temperature-humidity index have been shown to have only minor associations with colostrum quality (Zentrich et al., 2019).

Dairy cows are traditionally dried off 60 d before expected parturition and fed a controlled-energy diet throughout the whole dry period (NRC, 2001). However, researchers have proposed that dry period energy density may affect IgG content in first-milking colos-

trum (Mann et al., 2016; Dunn et al., 2017). Mann et al. (2016) found that feeding 150% of ME requirements during the dry period reduced colostral IgG concentration compared with feeding a control diet formulated to meet 100% of ME requirements. However, it is important to note that the diets in that study (Mann et al., 2016) only provided 91 and 123% of ME requirements in the control and treatment groups, respectively, during the week before calving. The energy restriction in the control group immediately before calving may have contributed to the differences in colostral IgG concentrations, as opposed to the energy oversupply in the treatment group. Aside from the aforementioned study, the majority of prepartum environmental and nutritional practices mentioned have not been investigated thoroughly and, as a result, concise and accurate recommendations on how to properly manage prepartum factors to improve colostrum quality (in terms of IgG) remain unclear (Zentrich et al., 2019).

Effect of Colostrum Components on the Neonatal Calf

Colostrum has a high fat content [5.7–6.4% vs. 4.3% in whole milk (**WM**); Dunn et al., 2017; Fischer-Tlustos et al., 2020] that is readily absorbed (Gooden et al., 1971) to support thermoregulation and the rapid metabolism of a newborn calf (Vermorel et al., 1983). Colostrum also contains a distinct fatty acid (**FA**) profile compared with WM, with higher levels of polyunsaturated and n-3 FA, and lower concentrations of saturated short-chain FA (Contarini et al., 2014; McGrath et al., 2016; O'Callaghan et al., 2020). Recent work indicated that feeding colostrum replacer supplemented with rumen-protected sodium butyrate (2.5% wt/vol) negatively influenced TPI (Hiltz and Laarman, 2019). Similarly, this result was observed with isobutyrate supplementation (Baumwart et al., 1977). The concentration of butyrate in colostrum is approximately half that of d-5 milk (O'Callaghan et al., 2020), possibly to avoid interference with gut closure, allowing for a prolonged period of intestinal hyperpermeability and facilitating TPI (Skrzypek et al., 2018). Conversely, feeding calves colostrum supplemented with 60 mL of a 1:1 mixture of fish and flaxseed oils (with 200 mg of α -tocopherol) high in n-3 FA (n-6:n-3 = 2.6:1) improved antioxidant status and reduced the accumulation of reactive oxygen and nitrogen species compared with calves fed a control colostrum (n-6:n-3 = 3.2:1; Opgenorth et al., 2020). However, it is important to note that the design of that study did not allow the authors to discern whether the observed effects were due to elevated n-3 FA, α -tocopherol, or their combination. Neonatal calves are subjected to high levels of oxida-

tive stress and a prolonged state of inflammation due to several factors, including dam stress before calving, dystocia, the onset of oxygen respiration, and the metabolic demands of adapting to the ex utero environment (Saugstad, 2003; Hulbert and Moisa, 2016; Ling et al., 2018). Elevated n-3 FA in colostrum (O'Callaghan et al., 2020) increases the pool of precursors used to produce anti-inflammatory compounds, thereby improving antioxidant capacity (Mavangira and Sordillo, 2018) and may counteract the oxidative stress experienced during the initial weeks of life.

In contrast to fat, colostral lactose content is $1.8 \times$ lower than that of WM (Fischer-Thustos et al., 2020). Yet, colostrum contains 15 to 72 times greater concentrations of the primary acidic oligosaccharides (OS) than WM (Fischer-Thustos et al., 2020). These OS are largely composed of a lactose core at their reducing end and are elongated by one or more sialic acid residues at the terminal end of the lactose molecule and can profoundly resist the low pH of the upper gastrointestinal tract and hydrolysis by pancreatic and mucosa-bound glycosidases (Engfer et al., 2000). Almost 50% of colostral OS are present in the colon of neonatal calves 12 h after feeding, demonstrating that the majority of OS reach the colon of the calf intact (Fischer et al., 2018). In vitro work has shown that the major OS in bovine colostrum and WM promote the growth of the beneficial bacterium *Bifidobacterium* in the intestinal tract (Yu et al., 2013) by inducing a substantial transcriptional response, enhancing its adhesion to enterocytes, and thus colonization in the neonatal gut (Kavanaugh et al., 2013). Importantly, IgG from bovine colostrum is highly glycosylated with sialic acid (Feehey et al., 2019), potentially derived from colostrum OS, which may interact directly with the IgG receptor site or indirectly stabilize the conformation of the receptor molecule (Gill et al., 1999), thereby providing a mechanism by which colostrum OS might influence IgG absorption in neonates. However, it is currently unclear if the specific glycosylation of IgG in colostrum directly facilitates IgG absorption in neonatal dairy calves.

Aside from the aforementioned bioactive components, colostrum contains an abundance of nonnutritive components that can influence the physiology and development of the newborn calf. For instance, colostrum contains microRNAs (miRNA) packaged in exosomes and microvesicles that are highly resistant to acidic environments and likely reach the small intestine in a biologically active state (Izumi et al., 2014; Benmoussa et al., 2016; Van Hese et al., 2020). Recent research in calves has demonstrated that of the 10 most highly expressed miRNA in the calf intestine, 6 were greater in colostrum compared with WM (Chen et al., 2010; Liang et al., 2014). The wide array of miRNA in co-

lostrum are hypothesized to positively affect development of the intestine and immune system regulation (Van Hese et al., 2020). Fresh colostrum also contains large amounts of maternal leukocytes (Godden et al., 2012) that can be detected in the blood, lymph nodes, and Peyer's patches of newborn calves after colostrum ingestion (Aldridge et al., 1998; Liebler-Tenorio et al., 2002; Reber et al., 2006). Maternal leukocytes in fresh colostrum have been implicated in reducing anemia and incidences of diarrhea (Novo et al., 2017). In addition, feeding whole versus cell-free colostrum increases vaccine responses in young calves (Langel et al., 2016), suggesting that the transfer of maternal cells in colostrum has both short- and long-term effects on the development of the calf's immune system. In addition to the aforementioned bioactive compounds, colostrum possesses supraphysiological concentrations of growth factors, hormones, nucleotides, and antimicrobial compounds that have been largely overlooked (see reviews by Blum and Hammon., 2000; McGrath et al., 2016; Fischer-Thustos et al., 2021), compared with IgG, in the past.

Transition Milk Feeding and Post-Day 1 Supplementation of Colostrum

The process of "gut closure," in which the neonatal intestine becomes impermeable to macromolecules in the gut, specifically IgG, occurs approximately 24 h after birth (Lecce and Morgan, 1962; Stott et al., 1979). Despite this, previous research has demonstrated positive effects of feeding colostrum or supplementing colostrum or IgG after the first day of life on calf health and development. For instance, supplementing calves with colostrum replacer to deliver 20 g of IgG in milk replacer (MR) from birth to 14 d resulted in lower mortality rates and reduced antibiotic treatments of diarrhea (Geiger et al., 2019). However, no effects on time to diarrhea resolution or mortality rates were observed in a similar study where diarrheic calves were supplemented with 20 g of IgG in MR daily for 14 d compared with diarrheic control calves fed a placebo supplement of similar nutritional value (Chung et al., 2019). In addition to feeding a colostrum replacer, supplementing pasteurized colostrum at 0.7 kg/d with 4.3 kg/d of WM reduced the prevalence of diarrhea and pneumonia (Kargar et al., 2020), and extending colostrum feedings for 14 d reduced the incidence of diarrhea and antimicrobial treatment (Berge et al., 2009). A short-term study demonstrated that feeding colostrum or a 1:1 colostrum:whole milk mixture (to simulate transition milk feeding) after the initial colostrum meal for the first 3 d of life increased small intestinal surface area and cell proliferation in certain

intestinal segments (Pyo et al., 2020) and increased concentrations of plasma glucagon-like peptide-1 (In-abu et al., 2019) compared with calves fed WM. It is possible that enhanced intestinal development in calves provided with extended colostrum feedings or transition milk may be responsible for the aforementioned positive health outcomes in previous studies (Berge et al., 2009; Kargar et al., 2020). However, it is necessary to elucidate whether specific bioactive compounds (as previously mentioned) or the synergistic effects of multiple colostrum bioactive molecules are responsible for improving both intestinal development and health status of young calves. Furthermore, current doses and duration of colostrum supplementation after the first day of life are variable and largely based on practical considerations. Determining the ideal supplemental dose and duration for optimizing calf and lifetime performance is required in future studies.

Future Directions

The relationship between prepartum nutrient intake (emphasized herein as energy intake) and colostrum composition requires further investigation. However, it is important that prepartum diets are designed to first promote a smooth transition to lactation for the dam and second promote calf TPI and overall development through consumption of high-quality colostrum. It is becoming increasingly clear that colostrum serves not only to provide TPI for the neonatal calf, but also to influence its growth and development. Transitioning calves gradually from colostrum to milk and extended supplementation of colostrum in the first weeks of life have beneficial effects on calf health and gastrointestinal development. Results from previous studies (Baumwart et al., 1977; Hiltz and Laarman, 2019; Opgenorth et al., 2020) have demonstrated that future research evaluating the specific effects of FA, including n-3 FA, in colostrum on calf immune function and oxidative stress is of interest. Furthermore, the role of additional bioactive compounds, including OS, miRNA, maternal leukocytes, hormones, and nucleotides, in colostrum and transition milk in neonatal development and immunity need to be tested directly in neonatal calves. These findings will allow the dairy industry to optimize its definition of “high-quality colostrum” and potentially create nonantimicrobial solutions to reduce the current high rates of morbidity and mortality experienced by young calves.

PREWEANING

Beyond the critical role of colostrum management in terms of health and survival of calves, choices re-

lated to the liquid feeding program in the preweaning phase also significantly influence calf development and future performance. Over the past decade, research in calf nutrition has highlighted the importance of feeding adequate levels of milk on preweaning growth and welfare (Soberon et al., 2012; Rosenberger et al., 2017). Although WM may have an optimal composition in relation to calf's requirements, MR provides a more consistent nutrient supply in terms of composition and percentage of solids (Hill et al., 2009). Approximately 35% of dairy calves in the United States are currently fed exclusively MR, and approximately 25% are fed a combination of MR and WM (Urie et al., 2018a); thus, calves fed MR represent a large part of the dairy calf population. Commercial MR formulations are highly variable, and recent research has highlighted the differences between conventional MR formulations and WM (Amado et al., 2019; Welboren et al., 2021). These formulations include MR with high lactose (40–50%; Wilms et al., 2020) or high protein (24–26% DM; Hill et al., 2008) and MR containing fat content close to that of WM (i.e., $\geq 23\%$; Amado et al., 2019; Berends et al., 2020).

Energy Requirements in Preweaning Calves

For young calves between 25 and 50 kg and fed only WM or MR, net energy maintenance requirements were set at $0.086 \text{ Mcal/kg}^{0.75}$ of live weight daily according to NRC (2001). Thus, a calf weighing 50 kg should receive 0.78 kg/d of DMI ($\sim 5.0\text{--}6.5 \text{ L}$) to reach an ADG of 600 g/d. Yet, over half of US farms provide dairy heifer calves with 4.0 to 5.0 L of milk/d (10% of birth BW; USDA, 2016). Compared with current trends in calf nutrition, these volumes are considered to represent a moderate to low plane of nutrition (Rosenberger et al., 2017). Calves provided with milk allowances of $\sim 10\%$ of birth BW daily display signs of hunger (Thomas et al., 2001; Jensen and Holm, 2003; De Paula Vieira et al., 2008) and have reduced growth (Jasper and Weary, 2002; Khan et al., 2011; Kiezebrink et al., 2015) compared with calves fed larger volumes of milk. Recent research has focused on feeding elevated planes of milk nutrition ($\sim 20\%$ birth BW; MacPherson et al., 2016; Welboren et al., 2019; Berends et al., 2020) to replace ment heifers, because higher preweaning ADG from increased milk allowance is associated with enhanced first-lactation and lifetime productivity (Soberon et al., 2012; Soberon and Van Amburgh, 2013; Gelsinger et al., 2016), as well as improved welfare (De Paula Vieira et al., 2008; Rosenberger et al., 2017). Calves fed ad libitum during the preweaning phase can achieve higher growth (823–1,100 g/d; Berends et al., 2020; Echeverry-Munera et al., 2021) than the upper ADG

range (600–800 g/d) presented in NRC (2001) recommendations, which are in line with those observed in calves reared with their dams (Flower and Weary, 2001). Maintenance energy requirements are influenced by feeding levels (Labussière et al., 2011) and models predicting energy requirements and growth of calves fed high planes of nutrition (~20% of BW) remain to be evaluated. Feeding greater volumes of liquid feed benefits calf health and performance, but it is unclear whether current MR formulations are adequate for high feeding rates in preweaning calves as MR presents nutrient imbalances when compared with WM.

Lactose Inclusion in Milk Replacer

Milk replacers often contain higher levels of lactose (~45 vs. 35% of DM) and lower levels of fat (~16 vs. 30%; Lee et al., 2009; Moallem et al., 2010; Amado et al., 2019) relative to WM. Prolonged intake of MR containing high levels of lactose was shown to result in impaired glucose homeostasis and insulin sensitivity in heavy veal calves older than 4 mo of age (Hostettler-Allen et al., 1994; Hugi et al., 1997). However, in calves 4 wk of age fed MR with either 37% or 44% lactose (up to 7.0 L of MR/d; 150 g/L), an intravenous glucose challenge showed that insulin sensitivity remained unchanged, and only minimal postprandial differences were detected regarding insulin and glucose dynamics (MacPherson et al., 2016; Stahel et al., 2019). Similarly, insulin sensitivity was unaffected when veal calves were fed MR containing 34 or 60% lactose for 13 wk at >10 L/d (Pantophlet et al., 2016a). Furthermore, replacing one-third of lactose with glucose, fructose, or glycerol did not affect insulin sensitivity compared with calves fed a MR containing 48% lactose for 55 d at a rate of 10 L/d (Pantophlet et al., 2016b). However, in the same study, calves fed MR with high lactose or MR with one-third of lactose replaced with glucose suffered from hyperglycemia and glucosuria. Despite the challenges in maintaining glucose homeostasis, these high-lactose and high-glucose MR formulations did not affect growth performance of calves (Pantophlet et al., 2016b; Wilms et al., 2020). However, gradual lactose replacement with glucose in an MR containing 47% lactose (% of DM) from 2 to 10 wk of age linearly increased mortality in calves (Wilms et al., 2020).

Beyond possible effects on glucose homeostasis, large amounts of lactose may challenge the gastrointestinal tract of young calves (Hof, 1980; Wilms et al., 2019), as lactose intake can exceed the absorptive capacity. Furthermore, galactose absorption may be reduced in the presence of high glucose concentrations (Hof, 1980). Incomplete digestion of lactose and inefficient galactose absorption increases the carbohydrate load entering the

lower intestinal tract. Unabsorbed nutrients and their fermentative products increase gut lumen osmolality, which may impair the ability of young calves to maintain the osmotic gradient for water and nutrient absorption, potentially resulting in osmotic diarrhea (Hof, 1980; Jodal and Lundgren, 1986). Feeding hypertonic MR with osmolality >400 mOsm/kg (compared with ~300 mOsm/kg in WM) can further challenge the absorptive capacity of calves and may compromise gut barrier function (Wilms et al., 2019). According to Hof (1980), daily lactose consumption should not exceed 10 g of hexose equivalents per kg of BW/d. This is equivalent to 6.7 L of MR (45% lactose, % DM; 15% solids) per day for a 45-kg calf.

Fat Inclusion and Fat Composition in Milk Replacer

Dietary fat from WM provides about 50% of total dietary energy, as well as essential FA to young animals. Tikofsky et al. (2001), Bartlett et al. (2006), and Hill et al. (2008) have all advocated for low-fat formulations, as higher MR fat inclusion increased tissue fat deposition, an effect that is proposed to impair mammary development (Sejrsen and Purup, 1997). However, although increased mammary gland fat deposition in weaned heifers is thought to be associated with lower milk production (Sejrsen and Purup, 1997), there is no evidence that mammary gland fat deposition in preweaning calves leads to adverse effects on milk production. Adipose tissue is highly metabolic and a potent endocrine organ (Frayn et al., 2003); thus, whether fat deposition is beneficial or detrimental for young animals requires further consideration. The degree of adiposity may critically determine beneficial or detrimental effects. Fat stores are mobilized during infection and may explain the association between nutritional status and mortality in infants (Kuzawa, 1998). Similarly, increased fat intake from liquid feed is associated with decreased mortality in preweaned calves (Urie et al., 2018b). In addition, calves fed MR with high fat (23% DM; 150 g/L) ad libitum required less therapeutic interventions from birth until 77 d of age (Berends et al., 2020), and calves fed MR with high fat (31% DM) restricted to 6.0 to 7.0 L/d (150 g/L) had lower preweaning fecal scores compared with calves fed MR with high lactose inclusion (>40% DM; Amado et al., 2019). Feeding higher levels of fat preweaning likely also improves later life performance. Moallem et al. (2010) showed that calves fed WM (29% fat) ad libitum had an increased milk production compared with calves fed an MR containing only 13% fat (12.5% solids). The authors attributed these effects to paracrine or endocrine factors of fat tissues on mammary parenchyma.

Beyond the lower fat content, MR differs substantially in fat composition (FA profile) and structure (triglyceride structure and fat globule size and structure) compared with WM (Esselburn et al., 2013; Hageman et al., 2019). Differences in FA composition are linked to the fat sources used in MR, which are primarily vegetable oils (e.g., coconut, palm, and rapeseed; Yohe et al., 2021) in Europe and animal fats (e.g., lard and tallow) in North America (Esselburn et al., 2013). Differences between WM and MR are relevant, as FA profile and triglyceride structure influence fat absorption (Hamilton and Raven, 1972) and gastrointestinal and immune system development in newborn animals (Guilloteau et al., 2004; Hageman et al., 2019). In infant nutrition, the milk fat globule membrane present in fresh breast milk plays a key role in metabolism and developmental processes (Gallier et al., 2015). In contrast, lipid droplets in MR do not contain milk fat globule membranes and are instead coated with casein and milk proteins (Lopez et al., 2015). The effect of fat composition in MR in relation to health and development in calves requires further investigation.

Protein Inclusion, Quality, and Source in Milk Replacer

The protein content of current MR formulations ranges between 20 and 28% DM, whereas WM contains 24.5% DM (Hill et al., 2008; Moallem et al., 2010; USDA, 2011). Increasing the protein content of isocaloric MR (>protein:energy ratio) increased growth rates and gain-to-feed ratios when fed at 10 to 15% of BW daily in Bartlett et al. (2006), and similar performance was reported in Jaeger et al. (2020). Furthermore, the protein gain to N intake was greater at a higher feeding rate, suggesting that producers could increase efficiency of N use by providing calves with greater amounts of MR (Bartlett et al., 2006). This is especially important during the first weeks of life, because N utilization for N retention is approximately 70% in calves between 50 and 100 kg and decreases as BW increases (Gerrits, 2019). As greater growth rates are targeted and achieved by feeding more milk, there is relatively more protein required for deposition of lean tissue. When protein intake is less than required for lean tissue growth, excess dietary energy will be stored as fat. Conversely, when protein intake exceeds requirements for lean tissue growth relative to energy intake, excess protein will be catabolized for energy production, resulting in inefficient use of dietary protein (Bartlett et al., 2006). Therefore, to optimize gain-to-feed ratio when feeding at ~15% of BW daily, it is recommended to feed an MR (when reconstituted at 12.5% DM with water) with approximately 22% CP (Bartlett et al., 2006). Optimal

levels of protein for calves following recent trends to allow for greater allowances of liquid feed (~20% of BW) in calf nutrition remains to be evaluated.

Protein source is similarly important because it can affect digestibility, subsequently inducing variations in calf growth performance (Raeth et al., 2016; Morrison et al., 2017). Milk proteins, such as whey protein concentrates, dry skim milk, or sweet whey powder, have greater digestibility (~94%; Guilloteau et al., 1986; Raeth et al., 2016) than vegetable proteins. Vegetable proteins include wheat and soy proteins and typically have a lower utilization in calves due to their imbalanced AA profile and the presence of antinutritional factors (Branco Pardal et al., 1995; Miqueo et al., 2017). However, a few highly processed sources of vegetable proteins, such as hydrolyzed wheat protein, may still represent suitable alternatives to reduce the dependence on dairy ingredients (Castro et al., 2016; Raeth et al., 2016). Furthermore, whey protein concentrate can be replaced by plasma protein (25% of CP) or plant peptide powder (25% of CP) without negatively affecting growth performance (Raeth et al., 2016; Morrison et al., 2017); however, more research is required to investigate how these protein and AA sources can profoundly affect growth and health.

Future Directions

Recent literature shows that milk feeding levels currently applied in the industry do not reflect the volumes that would be voluntarily consumed (Rosenberger et al., 2017; Berends et al., 2020; Echeverry-Munera et al., 2021). Despite positive effects on calf health and welfare, increasing planes of milk nutrition raises the question of whether current MR formulations are optimal (Amado et al., 2019; Echeverry-Munera et al., 2021). Interesting directions for future research in preweaning calf nutrition include the pathways in which MR macronutrient profile and micronutrient composition modulate calf health and development. Furthermore, the relation between fat sources (animal vs. vegetable oils) and fat globule size and structure (with or without fat globule membrane) on metabolism and immune function remain relatively unexplored. Last, the availability of dairy ingredients for MR manufacturing is market dependent, showing the need to explore alternative ingredients.

WEANING

Understanding the most efficient way to provide liquid feeding programs to calves is important during the preweaning phase, but of equal importance is the introduction of solid feed, which allows for the metabolic

and physiological transition from a nonruminant to a ruminant. A recent survey of UK dairy farms showed a lack of consensus regarding how best to transition calves from liquid to solid feed, with health and growth emphasized as the greatest concerns during the weaning transition (Palczynski et al., 2020). There is interest in introducing solid feed (i.e., starter/concentrates and forages) early in life to encourage early consumption and subsequent rumen growth and development to ensure a smooth weaning transition. However, regardless of WM or MR feeding level, solid feed consumption is low during the first 3 wk of life (Quigley et al., 2018). After the initial weeks of life, preweaning starter intake and liquid feed intake are inversely correlated, which may negatively affect preweaning growth (Gelsinger et al., 2016; Silva et al., 2019). Specifically, for each 100 g of MR DMI, starter DMI decreased by 13 g/d at 30 d of age and by ~93 g/d at 60 d of age (Silva et al., 2019). Thus, it is thought that feeding a high plane of WM or MR nutrition preweaning causes a decrease in growth rate postweaning, largely due to an inability to consume and digest sufficient quantities of starter for growth (Dennis et al., 2018; Quigley et al., 2018). It is important to note that not all energy and protein sources are going to provide the same amount of energy or required AA for calf and heifer growth. This review focuses only on the key concepts and, as such, will not discuss different energy and protein sources that may be used in calf and heifer diets. Further information can be found in the following reviews: Khan et al. (2016), Heinrichs et al. (2017), Kertz et al. (2017), and Gerrits (2019).

Weaning Strategies

Previously reviewed studies clearly show that gradual step-down protocols can be implemented to mitigate the negative side effects of weaning from a high plane of WM or MR (Khan et al., 2011, 2016; Meale et al., 2017a). These protocols also efficiently enable calves to maintain elevated growth rates resulting from high planes of milk nutrition from pre- to postweaning (Khan et al., 2007; Silper et al., 2014; Eckert et al., 2015). If higher planes of milk are fed, weaning should be delayed until after 8 wk of age to avoid weaning growth depression (Eckert et al., 2015; Meale et al., 2015, 2017b). In addition to age of weaning, implementation of a step-down protocol is essential, and recommendations generally agree that longer step-down periods are better for calves (>10 d gradual step-down; Sweeney et al., 2010). Furthermore, it is pertinent that the steps are gradual, because abrupt weaning is associated with growth depression (Khan et al., 2007; Sweeney et al., 2010; Steele et al., 2017). With the advancement of

automated feeders, it is now possible to step down calves from elevated milk levels by gradually reducing milk allowances over an extended period (Welboren et al., 2019). More importantly, we can also measure solid feed intake and use these measurements to determine the optimal onset of weaning (Benetton et al., 2019). Although these advancements in weaning strategies have been critical to the implementation of sound weaning strategies in the dairy industry, there remains a paucity of information around how the composition of solid feed (concentrate and forage) affects calf growth, health, and development, as well as how solid feeds can be tailored to fit these weaning strategies.

Energy Inclusion in Solid Feed Diets

The main sources of energy in calf feeds (i.e., liquid or solid) are carbohydrates and fat, with rapidly fermentable carbohydrates providing the majority of carbohydrate ME in solid feed. With respect to NFC (e.g., starch, sugar, and pectin) intake, Quigley et al. (2019a,b) determined that when calves consume <15 kg of cumulative NFC throughout life, ME intake is overestimated based on NRC (2001) equations, indicating that studies using the NRC (2001) model have likely overestimated ME availability. Quigley et al. (2019a,b) suggested that cumulative NFC intake has a greater relationship with total-tract digestibility of nutrients than calf age, MR intake, or daily nutrient intake. There may be specific situations in which the type or form of starter, or specific ingredients, may appear more appropriate than others. For example, Suárez et al. (2006a,b) demonstrated that a 49.3% NDF (% DM) and 10.8% starch (% DM) pelleted starter, compared with a 9.4% NDF (% DM) and 59.3% starch (% DM) pelleted starter, decreased epithelial thickness in the ventral rumen, but improved starter DMI, ADG, total rumen VFA concentration, and rumen weights in 12-wk-old veal calves fed starter at a maximum of 750 g/d. No differences in blood BHB concentrations at 12 wk were observed between the treatment groups, suggesting that age, as opposed to solid feed intake, is a critical factor in determining the onset of functional rumen epithelium development (as corroborated by Lane et al. (2000, 2002) and Yohe et al. (2019)). Metabolizable energy intake from solid feed (mainly as NFC in starter/concentrate) promotes overall growth and adequate rumen development, yet related health issues, such as ruminal or hindgut acidosis (Gressley et al., 2011; Gelsinger et al., 2020), are thought to compromise calf growth and health during weaning (Steele et al., 2017; Meale et al., 2017a). Gelsinger et al. (2020) reported that calves fed only pelleted calf starter (CS; 42.7% starch, 15.1% NDF, 57.8% NFC) or texturized

CS (35.3% starch, 25.3% NDF, 48.1% NFC) for 17 wk both experience some degree of ruminal acidosis but that calves fed pelleted CS experience reduced feed intake and BW gain and a higher degree of ruminal tissue damage. However, it is important to note that low rumen pH as a result of solid feed intake is common in calves that do not experience adverse health events as well (Li et al., 2012; Laarman et al., 2012; van Niekerk et al., 2021), and thus, requires further investigation. In contrast to using rapidly fermentable carbohydrates to increase energy in starters, increasing rumen inert fat content in starter diets from 3.3% fat (6.17 ± 0.10 Mcal of ME intake/d on DM basis) to 6.8% fat (7.06 ± 0.10 Mcal of ME intake/d on DM basis) using extrusion increased BW gain and starter intake (Berends et al., 2018). Diets were isonitrogenous (17.1% CP, % DM) in this study, indicating that overall energy supply is essential during weaning to support ADG as opposed to starter intake. Yet, body composition was not measured and, thus, it is unclear if BW gain was due lean or adipogenic tissue deposition.

Protein Inclusion in Solid Feed Diets

Similar to energy, dietary protein varies depending on the source and inclusion amount fed to calves. The NRC (2001) recommends that starters containing 18% CP (% DM) are adequate to promote maintenance and growth in calves. No differences in ADG (0.74 vs. 0.80 ± 0.06 kg/d; Stamey et al., 2012) were observed over a 10-wk period when feeding starter that differed in CP (19.6 or 25.5% CP, % DM), but not ME content (~ 3.2 Mcal/kg of DM), suggesting that even a large increase in CP:ME intake (~ 64 vs. 75 g of CP/Mcal of ME based on average of wk 5 and 7 for low and high CP, respectively) does not always confer growth benefits. However, it is important to note that a high CP MR (30.8% CP, % DM; 4.72 Mcal of ME/kg of DM) was fed in this study and may have influenced results. Yet, feeding a low CP MR (20% CP) resulted in no differences in ADG (0.63 – 0.67 ± 0.02 kg/d) in calves fed starter differing in CP:ME (67.4 – 71.4 g CP/Mcal of ME; Jaeger et al., 2020). Collectively, these results suggest there is little advantage to feeding starter containing more than 18% CP (% DM) to increase growth during weaning. It is important to note that many of these studies only consider CP supply, and not AA supply, which has been rarely studied in solid feeds (Quigley et al., 1985; Molano et al., 2020) but has great potential to optimize nutrient supply after weaning.

Utilizing protein for tissue and overall growth is valuable if used efficiently. Calves are largely inefficient at retaining N (Berends et al., 2014, 2015a), as N retention decreases by increasing protein intake via solid

feed in unweaned veal calves from 11 to 27 wk (i.e., 19% of improved N retention in the rumen due to urea recycling back to the rumen). Adequate rumen N is important for microbial growth. When CP consumption is only 93 g/kg of DM, compensatory urea recycling is not sufficient to support microbial growth and, thus, results in insufficient outflow of microbial CP from the rumen (Berends et al., 2015a). This suggests that a calf needs to consume a 21% CP (% DM) starter at a rate of ~ 443 g of DM/d, assuming a 4.1%/h rumen passage rate (Berends et al., 2015b), to maintain adequate N balance in the rumen to support microbial fermentation. Yet, forage consumption also contributes to dietary CP intake, with alfalfa hay and barley straw containing $\sim 16.6\%$ and $\sim 4.2\%$ CP (% DM), respectively (Castells et al., 2012). Considering the observation of approximately 13% DMI (pre- to postweaning of starter and forage) of alfalfa hay by Castells et al. (2013) and the 93 g of CP/kg of DMI from solid feed (50% concentrates, 25% corn silage, and 25% straw on a DM basis) noted by Berends et al. (2015a) required to support rumen microbial growth, alfalfa hay would need to provide approximately 12 g of CP/kg of DMI (Castells et al., 2012). If microbial protein synthesis is not optimized during weaning, the starter/concentrate/forage becomes the primary source of protein and AA in the rumen. The factors that contribute to microbial protein synthesis have been well researched in mature dairy cows (Clark et al., 1992) but have been rarely studied in starter feeds for calves (Quigley et al., 1985). Even though it can be technically challenging, it is important to estimate microbial protein synthesis in future experiments and develop a deeper understanding of how it changes during weaning to supply the optimal level of high-quality protein to the calf.

Future Directions

Numerous advancements over the past decade have improved our approach to weaning age and step-down strategies depending on the milk feeding level. However, future research should aim to refine the specific combination of WM and MR and specific starter/concentrate/forage ratios to optimize calf growth and development. Understanding total DMI, ME, protein, and AA intake is a critical first step, but determining how to appropriately balance the amount of ME and protein supplied in both liquid and solid feed based on plane of WM/MR, and further acknowledging their interactions, will further improve efficiency during the preweaning and weaning periods. Improving equations in our nutritional models to predict solid feed carbohydrate digestion and microbial protein synthesis at different stages of weaning would also be highly valu-

able. With automated feeding of liquid and solid feed, tailoring individualized weaning strategies to maintain nutrient intake and growth during weaning is now possible but, unfortunately, rarely implemented.

PREPUBERTAL AND POSTPUBERTAL PHASES

After fully transitioning to solid feed, there are many different strategies that can be employed to ensure proper development during the next crucial stages of life (i.e., puberty, pregnancy, calving). The established guidelines for heifers in our industry is to target first calving between 22 and 24 mo at $0.82 \times$ mature BW (Van Amburgh et al., 2019); however, recent data suggests that a target of 0.73 to $0.77 \times$ mature BW increases milk production in first lactation without compromising long-term production (Han et al., 2021). Certainly, heifer rearing targets and requirements are not well understood during the prepubertal and postpubertal phases and may be influenced by nutrition earlier in life. Several recent reviews (Heinrichs et al., 2017; Van Amburgh et al., 2019; Erickson et al., 2020) have compiled management strategies proposed to optimize heifer calf nutrition from prepuberty to first calving to reduce rearing costs, optimize age at first calving, and improve milk production. Although the developmental plasticity at this stage of life is lowest (Figure 1), some examples have illustrated how altering nutrition programs can affect future productivity. For example, Ford and Park (2001) showed that Holstein heifers receiving multiple nutrient restrictions during the prepubertal, pubertal, and gestation periods, followed by realimentation to normal diets, increased milk production in first lactation. Few replacement heifer studies have investigated growth and development past weaning, which is surprising given that the prepubertal period after weaning represents the highest feed efficiency for growth (Bach and Ahedo, 2008). Furthermore, several key areas still need to be addressed, including when to transition calves from high-energy and protein-concentrate diets to lower energy and high-protein forage diets in the prepubertal period, as well as determining the optimal energy and protein provisions to maximize growth and development before and after puberty.

Energy Provision

Transitioning prepubertal heifer calves after weaning from high-concentrate diets rich in rapidly fermentable carbohydrates to forage-based diets is a traditional strategy to control energy intake and avoid excessive adipogenesis. It has been suggested that high-concentrate and energy diets during the prepubertal stage of

life can cause an accumulation of adipose tissue in the developing mammary gland and may ultimately lead to reduced milk yield later in life (Sejrsen and Purup, 1997; Van Amburgh et al., 2019). For this reason, the inclusion of high amounts of concentrate in the prepubertal diet has been approached cautiously. However, excessive forage provision after weaning limits dry feed intake and growth due to an apparent limit of NDF intake as a percentage of BW (defined as 1% of BW by Hoffman et al., 2008 and Mitchell and Heinrichs, 2020). Reducing forage particle size may mitigate reductions in total DMI, but most importantly forage provision at weaning should be controlled to increase overall dietary intake. Forage provision can be affected by age, nutrient composition, and physical form of both concentrate and forage and is important for rumen buffering and physical abrasion of the rumen wall, even when fed in low amounts (5% of diet; Suarez-Mena et al., 2016). Calves fed high-concentrate diets (85%) for the months immediately following weaning can achieve high ADG (>1.5 kg/d; Groen et al., 2015; Rosadiuk et al., 2021). However, the optimal duration of high-concentrate feeding and how this may affect fat deposition, feed efficiency, and future milk production is still unknown.

The most important variable that can be manipulated in replacement heifers during the prepubertal-to-pregnancy stage is growth rate. Growth rate can influence breeding age, age at first calving, lifetime productivity, and feed costs (Heinrichs et al., 2017; Van Amburgh et al., 2019; Erickson et al., 2020) and will be the main focus of this section. Several studies have investigated the effect of prepubertal ADG on milk production. Zanton and Heinrichs (2005) and Heinrichs et al. (2017) stated that ~ 0.8 kg/d is the optimal prepubertal growth rate. However, to our knowledge, the studies reviewed by Heinrichs et al. (2017) fed low to moderate planes of nutrition preweaning, which may have influenced the postweaning growth rates of prepubertal heifers. For instance, calves fed a high-protein MR [30.6% CP and 16.1% fat (% DM) fed at 2.1% of BW] and starter (24.3% CP; % DM) diet to achieve ADG of 0.68 kg/d achieved puberty earlier (270 ± 5.8 d and 287 ± 5.5 kg of BW) than calves fed a conventional MR [21.5% CP and 21.5% fat (% DM) fed at 1.2% of BW] and starter (19.9% CP; % DM) to achieve 0.45 kg/d ADG, in which puberty was not attained until BW was >300 kg (Davis Rincker et al., 2011). Yet, this difference only led to a tendency for fewer days to conception and did not affect days to parturition or lactation (i.e., average milk through 150 DIM, projected 305-d milk, or milk component yields). Thus, plane of milk nutrition may not have a large effect on the primary outcomes associated with the efficiency and profitability of dairy operations (i.e., age at first calving). However, that study is

one of the first to investigate the effect of preweaning nutrition on puberty onset and parameters directly associated with the profitability of dairy operations and thus requires additional work. Further, there are limited studies with sufficient replication following calves from preweaning to pregnancy, with a lack of evidence showcasing different protein and energy intakes during both phases.

A recent study observed that increased planes of nutrition during both the pre- and postweaning periods resulted in greater ADG and indicators of growth and development in heifer calves up to 25 wk of age (Rosadiuk et al., 2021). The increased preweaning planes of nutrition had minimal influence on growth performance postweaning, regardless of the improved indicators of growth and development in the preweaning stage. As reported in companion manuscripts (Bruinje et al., 2019, 2020), increased pre- and postweaning planes of nutrition resulted in advanced reproductive development. The increased preweaning plane of nutrition resulted in enhanced LH pulses at wk 15, increased circulating leptin concentrations (Bruinje et al., 2019), and a greater number of class 2 ovarian follicles (Bruinje et al., 2020) during the prepubertal phase. The increased planes of nutrition postweaning resulted in increased endometrial thickness, follicular size, number of class 3 follicles in the prepubertal phase (Bruinje et al., 2020), greater likelihood of achieving puberty by 30 wk of age (Bruinje et al., 2019), and increased antral follicle population in the postpubertal phase. Both the high pre- and postweaning nutritional planes had elevated energy and protein content; thus, the respective effects of plane of energy or protein on growth and reproductive development cannot be distinguished. Further research is warranted to investigate how protein or energy content during the preweaning, postweaning, and prepubertal stages affect the onset of puberty and subsequent reproductive performance in heifer calves. Furthermore, a better understanding of early-life factors influencing the ideal body size, composition and age that heifers should enter the breeding program for optimal performance is crucial. For instance, if too much forage is added to the diet in the months postweaning, it may decrease ADG (by 0.5 kg/d; Groen et al., 2015) and could ultimately delay age at puberty (Bruinje et al., 2020). This potential delay in puberty onset may increase nonproductive days on feed, ultimately affecting replacement heifer rearing cost. Therefore, maximizing growth rates during the prepubertal phase when feed efficiency is elevated could be an effective means of maximizing growth before the onset of puberty, but the long-term consequences on growth, development, and milk production need to be investigated.

Fibrous feedstuffs are often incorporated into the diet of prepubertal heifers as a means of manipulating intake and ADG (Akins, 2016; Erickson et al., 2020). One strategy to aid in the prevention of overconditioning heifers from preweaning through pregnancy is to include a higher amount of low-quality forage (e.g., grass hay, wheat straw, or other forage sources) in the diet (Erickson et al., 2020). This has proven successful in achieving desirable ADG in weaned heifers (0.92 ± 0.04 kg/d of gain) limit-fed a TMR with grass hay and starter (Mitchell and Heinrichs, 2020), as well as pregnant heifers (0.96 and 1.04 ± 0.07 kg/d of gain) fed a TMR ad libitum with either alfalfa haylage or corn silage and 32.1% alfalfa stemlage or 31.3% alfalfa or corn silage and wheat straw (Su et al., 2017). Hoffman et al. (2008) demonstrated maximum NDF intake at 1% BW from approximately 4 mo of age to first calving in Holstein and Holstein $\times$ Jersey crossbred heifers. Mitchell and Heinrichs (2020) found that 4-mo-old Holstein heifers consumed NDF at 0.89% of BW, whereas pregnant heifers (starting BW: 487 ± 0.8 kg; final BW: 543 ± 4.1 kg) consumed NDF at 0.86 to 0.91% of BW when fed wheat straw and alfalfa stemlage, respectively (Su et al., 2017). Further, the proportion of undigested NDF is higher in straw than in other forages (Kahyani et al., 2019) and has a negative effect on DMI (Mertens, 2016). A recent study investigated forage provision after weaning at 6 wk until 16 wk of age and noted depressed feed intake and growth when forage inclusion is $>10\%$ (Mitchell and Heinrichs, 2020). Thus, it is important to consider NDF, and perhaps undigested NDF, in the future when formulating heifer diets to achieve optimal digestibility and growth.

Protein Requirements

Similar to weaning, the amount of protein fed to calves during the prepubertal and pubertal periods varies in the dairy industry. Gabler and Heinrichs (2003) assessed different CP:ME ratios fed to 4-mo-old heifers utilizing the same amount of forage (corn silage and grass hay), but differing the levels of concentrate ingredients in the diet to increase the CP:ME of the diet from 48.3 g of CP/Mcal of ME to 59.1, 67.5, and 76.5 g of CP/Mcal of ME. The amounts offered were adjusted weekly to allow for 0.8 kg/d ADG for all treatments. The study found a linear improvement in feed efficiency (kg of feed intake/kg of BW gain) with increasing CP:ME intake. These results suggest that feeding adequate CP relative to ME is important for heifers postweaning. Furthermore, this research corroborated previous results demonstrating that a lower NSC:RDP allowed for more efficient protein use for

growth in calves 3 to 5 mo of age (g/g NSC/RDP for CP:ME ratios were 48:4, 59:3, 68:3, and 77:2; Casper et al., 1994). Yet, the optimal timeframe for reducing NSC intake relative to forage intake remains an important question. Gabler and Heinrichs (2003) and Casper et al. (1994) showed that these changes can be made as early as 3 to 5 mo of age, as long as adequate CP is supplied. This is supported by Mitchell et al. (2020), where calves ~3 mo of age offered starter and grass hay *ad libitum* as separate components reached a plateau in forage consumption (around 0.28 kg/d, which was 8% of total DMI), whereas starter intake continued to increase throughout the 14-wk study. This unrestricted starter intake for extended periods likely increased microbial protein supply to support growth rates higher than the commonly recommended ADG of 0.80 kg/d to achieve maximal first-lactation milk yield (Zanton and Heinrichs, 2005). More research is required to understand how to maximize microbial protein synthesis during the transition from high-concentrate to high-forage diets to supply prepubertal calves with the protein and AA needed to support growth and development.

Future Directions

The main goal of the prepubertal and pubertal periods is to achieve appropriate weight gain to reach age at first calving as early as 22 mo, while balancing feed input and feed efficiency (Akins, 2016; Heinrichs et al., 2017). As noted in the review by Erickson et al. (2020), this may be achieved through precision feeding, but further evidence showcasing how to effectively implement these strategies is needed. Recent work suggested that a transition from a high-concentrate diet to a high-forage diet should not occur in the initial months following weaning (Rosadiuk et al., 2021). However, research uncovering the optimal time to transition weaned calves to a high-forage diet is lacking. One major consideration is the high ADG and feed efficiencies reported during the prepubertal period, which may more effectively maximize calf BW than the milk phase of nutrition. Furthermore, the level of protein to include with a high-NDF forage to prevent nutrient waste, promote lean tissue gain, as well as support protein requirements during pregnancy, remains a major knowledge gap that requires attention.

SUMMARY

There has been great momentum and global interest in the field of calf research, especially around the potential to developmentally program calves in early life to increase productivity and health. However, several knowledge gaps remain related to nutritional manage-

ment in each developmental phase (Figure 1) that significantly limit this potential. Expanding our understanding of energy and protein dietary requirements and composition will ultimately improve calf growth and development. Therefore, there is a strong need to integrate this dietary knowledge with health research to mitigate incidences of disease and disorders in calves.

The momentum in calf research has resulted in a vast number of recently published articles. Despite this increase in publications, incomplete reporting in primary studies is unfortunately common in calf and heifer research, making it challenging to construct systematic reviews and meta-analyses (Winder et al., 2018). The dairy science community, including authors, reviewers, and editors, should follow reporting guidelines developed through expert consensus to improve reporting outcomes from livestock trials (Sargeant et al., 2010; Winder et al., 2019). Improved reporting will ultimately lead to a better understanding of the efficacy of nutritional strategies at each stage of life, thereby increasing the value of calf research. Another key experimental point that requires consideration in calf research is the long-term consequence of the imposed dietary treatments on lifetime events. A comprehensive understanding of how nutrition affects developmental programming is only possible if we characterize the effects of early-life treatments, along with follow-up measurements throughout all stages of life, including first lactation. These experiments are challenging because of biological replication constraints in research facilities and the lack of infrastructure to support studies characterizing lifelong events. Nevertheless, strategies to overcome these challenges need to be developed to generate critical knowledge pertaining to the long-term effects of nutritional strategies.

In closing, we have highlighted nutritional aspects, ingredients and composition, and feeding and management strategies that influence fetal and calf development and growth (summarized in Figure 1). It is clear that there is great momentum toward and interest in understanding these effects to improve heifer calf production, efficiency, health, and welfare. However, each life stage requires different nutritional strategies that may or may not have carryover effects or lead to different long-term outcomes, or both. Therefore, it is important to continue pursuing research investigating optimal nutritional strategies to improve calf performance and health without compromising cost efficiency.

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