Nutrition, rumen health and inflammation in the transition period and their role on overall health and fertility in dairy cows


Abstract

Transition is a stressful period and critical for the entire cow's productive lifespan and reproduction. Optimal feeding management during transition period enables smooth metabolic adaptation to the initiation of lactation. Major nutritional challenge during this period is the urgent need to counteract the drastic deficits in energy and nutrients of the early-lactating cow. This is primarily done by inclusion of large amounts of concentrates in the diet during early lactation, causing major dietary imbalances with utmost importance for rumen health. Proper feeding management targeting rumen health in the transition period improves nutrient degradation and the net supply with energy and key nutrients of the host while preventing systemic disturbances and inflammation, events which are instrumental for cow's overall health and reproductive performance. The review provides insights into the role of, and gives practical hints regarding diet balancing efforts and feeding management strategies targeting rumen health and systemic inflammation during the periparturient period with the aim to enhance cow health and fertility.

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The transition period (i.e., the time between 2 weeks before and 4 weeks postpartum) is critical for health, fertility, and productivity of dairy cows (Kim and Suh, 2003; Garverick et al., 2013; Esposito et al., 2014). This period is characterized by drastic metabolic, immune and endocrine changes, rendering cows extremely susceptible to diseases (Lacetera et al., 2005; Sordillo, 2005; Ospina et al., 2010a,b). Feeding
management is crucial for metabolic adaptation of transition dairy cow (Loo et al., 2007; Kraugnard et al., 2013; Roche et al., 2013). The major nutritional challenge in the periparturient period is to meet increasing requirements in energy and key nutrients while voluntary feed intake potential of the periparturient cows is limited (Grummer, 1993). This renders the vast majority of cows developing negative energy balance (NEB) and deficits in key nutrients early postpartum. To alleviate this discrepancy in intake and requirements for energy and nutrients, large amounts of concentrates are fed, often at the expense of fiber-rich forages, which cause major dietary imbalances (i.e., lowered concentration of physically effective fiber) with critical importance for rumen health (Zebeli et al., 2012a).

A large body of evidences indicates that poor rumen health results in systemic inflammation (Plaizier et al., 2012; Zebeli and Metzler-Zebeli, 2012) and greater risk of developing other disorders such as laminitis, abomasal displacement, bloat, off-feed, and ketosis (Plaizier et al., 2008; Ametaj et al., 2010a; Bradford et al., 2015). These events aggravate the supply with energy and nutrients needed to support key biochemical processes related to milk production and reproduction (Khaoa-ard and Zebeli, 2014). Because homeorhetic metabolic processes favor milk production rather than body reserves and reproduction in early lactation (Drackley and Cardoso, 2014), the fertility is the most affected physiological process from dietary imbalances and their resulting disturbances during the transition period. Indeed, during the last decades there has been an alarming decline in fertility of dairy cows with strong consequences for the profitability of dairy farms in most countries (Butler and Smith, 1989; Lopez et al., 2004; Dobson et al., 2008).

The reproductive performance of the cow is a multifactorial variable, whereby cow genetics, nutrition, uterine and systemic health, management and heat control, bull fertility and practices associated with artificial insemination seem to play a role (Ball and Peters, 2004). In particular the events associated with the first 8 weeks of lactation in cows are critical for subsequent success or failure of establishing pregnancy during the breeding period (Lucy et al., 2014). From a nutritional standpoint, preparation for a successful reproduction starts before calving, when the cow is dried off (Drackley and Cardoso, 2014). Indeed, a large body of evidence and several comprehensive review articles emphasize the role of nutrition during transition period in reproduction (Butler and Smith, 1989; Grummer, 1993; Butler, 2005; Drackley and Cardoso, 2014; Lucy et al., 2014). However, the role of feeding with emphasis on rumen health and reproduction during this period has not been described so far. This review article aims to provide an overview of the role of nutrition targeting rumen health and metabolism during the transition period in overall health and reproductive performance in dairy cows.

2. Nutrition, rumen functioning and health

2.1. Role of rumen functioning in energy and nutrient supply

The rumen is a classical host-microbial ecosystem that enables cows to convert the complex dietary carbohydrates that cannot be digested by mammalian enzymes into short-chain fatty acids (SCFA) as the main energy source for the host (Aschenbach et al., 2011). Besides generating energy, proper functioning of the rumen is critical for the synthesis of microbial protein and vitamins, most importantly B-vitamins which are crucial in energy metabolism (National Research Council, 2001). Because absorption of SCFA (Aschenbach et al., 2011) and several key minerals takes place mainly in the rumen (Tomas and Potter, 1976; Schröder and Breeves, 2006), it is reasonable to assume that proper development, health and integrity of the rumen epithelium is also important in supplying the host with energy and essential minerals. In addition, disturbed rumen conditions often result in incomplete degradation, thus shifting digestion processes distally to the rumen (Metzler-Zebeli et al., 2013). As a consequence, suboptimal absorption and digestion processes and an increased passage rate of the digesta as well as diarrhea-like conditions (Li et al., 2012) likely occur, causing suboptimal nutrient supply and reduced feed efficiency (Khiaoa-ard and Zebeli, 2014). Also, the risk of mycotoxin contaminations to impair rumen microbiota, and thus the risk of mycotoxins to cause a mycotoxin syndrome and to be transferred from feed-to-milk (carry-over), increases when rumen functioning is disturbed (Santos and Fink-Gremmels, 2014). This explains why cows in the transition period are considered to be particularly sensitive to the exposure to feeds contaminated with molds, fungal spores, and mycotoxins (Fink-Gremmels, 2008).

Fig. 1 provides an overview of the dietary factors (i.e., the balance of physically effective fiber and easily degradable carbohydrates) that help maintaining proper rumen functioning, rumen health and epithelial integrity, while assuring absorption and metabolism of the absorbed key metabolites for the host to be used for maintenance, production and reproductive processes. A well functioning rumen promotes symbiosis, nutrient degradation and also SCFA absorption, resulting in a large fermentation output that can be used by the cow for gluconeogenesis and other important biochemical processes such as milk component synthesis. From the standpoint of energy supply of the cow, propionate generated in the rumen is highly important for gluconeogenesis (Fig. 1). Propionate is produced by rumen microbes mainly through fermentation of readily fermentable carbohydrates, particularly rumen degradable starch (RDS). This type of starch is readily degradable in the rumen supplying large amounts of propionate for gluconeogenesis when RDS-rich diets are fed to lactating cows (Aschenbach et al., 2010), in particular during early lactation. Rapid ruminal starch degradation, in turn, alters the composition and metabolic activity of the rumen microbiota, mostly against fibrolytic- and in favor of amylolytic species (Fernando et al., 2010; Mao et al., 2013), leading to accumulation of lactate with consequences for rumen health and microbial symbiosis such as subacute ruminal acidosis (SARA) and severe dysbiosis (Plaizier et al., 2008; Khafipour et al., 2009; Saleem et al., 2012). Therefore, a healthy diet for cows primarily targets the rumen microbiota, whereby diets low in physically effective fiber (peNDF) and in excess of RDS should be avoided. In this respect, Table 1 provides recommendations existing for RDS from grains depending on the amount of peNDF expressed inclusive particles >1.18 mm (peNDF-1.18) and dry matter intake (DMI) of the cows. Thus, the amount of RDS in the diet depends on the content of peNDF-1.18 and DMI of cows (Table 1), whereby increasing peNDF-1.18 contents and decreasing DMI levels seem to improve ruminal tolerance of RDS, hence allowing greater inclusion of RDS in the diet of dairy cows. This interactive association between RDS and peNDF and DMI indicates that both latter factors should be accounted for to determine the adequate level of RDS in the diet.

Among grains commonly used in cattle diets, barley and wheat are richer in RDS than corn (Offner et al., 2003), suggesting corn as a grain of choice during early lactation. Also, contents of RDS can differ significantly between varieties with amylose-rich varieties having lower amounts of RDS (Silveira et al., 2007). Because of the importance of controlling RDS content in the cow’s diet, substantial research efforts have been conducted over the years to lower RDS proportion of dietary grain by using various feed technological approaches (Deckardt et al., 2013). Among those, chemical processing has been suggested recently to lower ruminal degradation of RDS-rich grains such as barley (Iqbal et al., 2009, 2010; Deckardt et al., 2013, 2014). These studies showed that processing of barley with organic acids and heat improved rumen health, as indicated by higher rumen pH values, decreased concentrations of rumen endotoxin and higher milk fat contents, and metabolic health status (i.e., higher glucose and insulin levels and lower acute phase response) of the cows (Iqbal et al., 2009, 2010, 2012a,b) as well as ameliorated in vitro ruminal fermentation, such as lowered concentrations of total SCFA but increased proportions of propionate (Deckardt et al., 2015), suggesting benefits of feeding the treated barley grain with low RDS content to cows during the transition period.
Particularly in early lactation, hepatic gluconeogenesis is a crucial process to support glucose homeostasis, because the alimentary supply of glucose is largely insufficient to meet the demands (Aschenbach et al., 2010), in particular for milk production (Fig. 1). Another approach to stimulate glucose pools in early lactation cows is to feed grains with high rumen undegradable starch (RUS) (Fig. 1), such as corn versus barley or wheat, or feeding processed grains with lower starch degradability (Zebeli et al., 2010a). This does not only improve glucose pools and its availability; by doing so rumen metabolism and generation of protons are relieved too, because a proportion of the grain starch is not degraded in the rumen but in small intestine. This is helpful in the prevention of ruminal acidification (Aschenbach et al., 2011). On the other hand, RUS digested in the duodenum leads to greater net glucose absorption for the host (Fig. 1). The increase in the availability of glucose might prevent excessive lipolysis and keep concentration of non-esterified fatty acids (NEFA) and beta-hydroxybutyrate (BHBA) at rather normal levels. This metabolic condition is helpful to prevent lipolytic-related metabolic disorders such as liver lipidosis and ketosis, typically observed during early lactation (Ospina et al., 2010b), with positive influence in reproduction performance (Lucy et al., 2014). Nevertheless, shifting the starch digestion from the rumen to the small intestine increases portal-drained visceral glucose absorption, which in turn lowers net glucose supply to peripheral tissues (Reynolds et al., 1998; Huntington et al., 2014). However, this increased portal-drained visceral tissue use of glucose is not associated with an increase in energy use by the respective tissue (Reynolds et al., 1998), indicating that other energy substrates are conserved.

Feeding of glucogenic diets (i.e., RUS-rich diets) is discussed controversially regarding their direct effects on fertility; they seem to initially stimulate resumption of ovary activity and ovulation but appear to impair the oocyte development competence (Garnsworthy et al., 2009; Drackley and Cardoso, 2014), which need to be considered in the feeding management of fresh vs. high lactation cows. During the time of ovulation in the peak of lactation, it is therefore important to support energy supply (glucose generation and glucose pools) mainly by enhancing intestinal net glucose supply by feeding more RUS. Indeed, this strategy in favor of RUS vs. RDS feeding is more appropriate during early lactation because of the highest sensitivity of rumen health during this period. After ovulation, production of glucogenic precursors in the rumen via propionate seems to be the best choice. For the latter, it is important to stimulate the growth and integrity of the rumen epithelium, since SCFA are absorbed directly across the multilayer epithelium of the reticulorumen mainly by the help of monocarboxylate transporters (MCT), such as MCT1 and MCT4, found in the basolateral and apical sides of the rumen wall (Fig. 1). It has also to be mentioned that the absorption of SCFA is not only instrumental in supplying energy to the host (almost 60–70% of energy demand; Aschenbach et al., 2011). While the absorption of SCFA (mainly acetate) ensures direct recovery of energy substrates from the rumen into the metabolic pool of the animal, this absorption also regulates the intraruminal milieu and pH by the extraction of protons together with SCFA (Aschenbach et al., 2011), hence lowering the risk of rumen fermentation disorders (Fig. 1). In fact, cattle develop rumen metabolic disorders associated with severe dysbiosis when rumen buffering capacity cannot keep pace with the

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**Fig. 1.** Graphical presentation indicating the role of balanced nutrition in rumen pH regulation and proper functioning as well as in the contribution to gluconeogenesis and glucose pools with implications in health and fertility in cows: BHB, β-hydroxybutyrate; Ac-ac, acetoacetate; RDS, rumen degradable starch; RUS, rumen undegradable starch; peNDF, physically effective neutral detergent fiber; SCFA, short-chain fatty acids in protonated (HSCFA) or ionic (SCFA-) form; HCO₃⁻, bicarbonate, NEFA, non-esterified fatty acids; MCT, monocarboxylate transporters; SGLT-1, sodium coupled glucose transporter 1 and GLUT-2, facilitated glucose transporter 2.
accumulation and/or neutralization of the SCFA (Aschenbach et al., 2011). Therefore, the inclusion of grain in the diet has to be tempered with the capacity of the rumen to neutralize the generated proton and avoid rumen acidification. In addition, feeding of the rumen microbes should target a gradual adaptation of the absorptive morphological and intracellular structures (both papilla size and production and functionality of MCTs), for which a minimal time of 2–3 weeks is necessary (Bannink et al., 2012). Thus, in practical terms, it is necessary to introduce a plan of gradual increase of the grain during transition period of at least 2–3 weeks before the maximal amount is fed to cows during early lactation. The same practice is true when a new diet/grain with greater rate and extent of fermentability is introduced in the feeding of dairy cows.

2.2. Feeding management to maintain rumen health during transition period

Due to its high microbial diversity and density as well as the large epithelial surface, the rumen plays a key role not only in digestion but also in modulatory functions of the host’s immune responses, and overall health (Zebeli and Metzler-Zebeli, 2012). When the symbiotic relationship in the rumen is disturbed, rumen health becomes a systemic concern of the inner homeostatic mechanisms. Besides the luminal environment, the integrity and health status of the rumen epithelium is also a very important factor in cattle health. In addition to their central metabolic roles, rumen epithelial cells are the first line of defense against hostile rumen conditions such as acidic pH, high osmotic pressure, and harmful microbial-derived metabolites, in particular when ruminants are fed energy-rich diets (Chen et al., 2012; Hollmann et al., 2013). The integrity of the rumen epithelium is usually maintained by the interplay of certain intercellular structures called tight-junctions and gap junctions (Penner et al., 2011). However, during early lactation histological, morphological, and transcriptomic adaptations of the rumen papillae take place. In this context, Steele et al. (2015) recently observed dramatic changes in the histology and morphology of the rumen epithelium during the onset of lactation and the concomitant enhancement of the energy concentration of the diet. Besides accelerated cellular differentiation and desquamation of keratinocytes, differential regulation of several cell junction genes and growth factors were observed during the adaptation to lactation (Steele et al., 2015).

In general, proper feeding of cows during the transition period is important to maintain integrity and support rumen health. For this, besides diet composition with sufficient peNDF (Zebeli et al., 2012a; Fig. 1), the principles of smooth adaptation feeding during close-up and fresh lactation are highly important (Drackley and Cardoso, 2014). With respect to the amounts of peNDF in the diet needed to prevent ruminal pH depressions in cows, there are recommendations for peNDF$_{1.18}$, in particular when diets are fed as total mixed ration (TMR) and the concentrate is not pelleted form (Table 1), and peNDF$_{8}$ (peNDF expressed inclusive of particles > 8 mm) especially when diet is fed as partial TMR or concentrate is in pelleted form (Table 2). Accordingly, the amount of peNDF needed to prevent ruminal pH depression below 6.2 strongly depends on the content of RDS or total starch of the diet, and also on DMI level of the cows, indicating that the requirements of dietary cattle for peNDF are not static. These requirements change with the amount of easily fermentable substrate (i.e., RDS or total starch) and total amount of substrate ingested (i.e., DMI). Thus, greater contents of RDS or total starch in the diet as well as greater DMI result in greater requirements of the cows for peNDF. On the other hand, excessive amounts of peNDF (i.e., >32% peNDF$_{1.18}$ or >18% peNDF$_{8}$) result in lowered maximal feed intake potential of the cows which should be avoided, in particular during early lactation due to the energy deficit of the cows during this time. However, because the voluntary DMI of cows during early lactation (at least until 4–5 weeks postpartum) typically doesn’t go beyond 18 kg DM/d, maximal amounts of 25–32% peNDF$_{1.18}$ are needed in the diet, assuming RDS contents from grains of 16–20%, respectively (Table 1). Likewise, for the same voluntary DMI level (up to 18 kg/d), early lactating cows will require 16–18% peNDF$_{8}$ in their diets to maintain ruminal pH at about 6.2, assuming a total starch content of 22–26% in the diet (Table 2). A daily mean ruminal pH of 6.2 is a safe threshold against SARA, allowing optimal ruminal functioning (Zebeli et al., 2008, 2010c).

During the last 2–3 weeks of gestation (close-up period) the grain level is gradually increased, and the diet is adjusted to increased requirements for energy and nutrients like metabolizable protein, vitamins, and minerals (Drackley and Cardoso, 2014). While avoiding excesses of energy intake in order to control body condition scoring (BCS) around parturition (Drackley and Cardoso, 2014), increasing amounts of grain during the close-up period allow a smooth adaptation of the rumen epithelium structures and microbiota to grain-rich diets after parturition (Fig. 1).

Besides diet composition, feeding management also becomes very important during the transition period. For example, ingestion of large meals in short time predisposes cows to rumen disorders because rumen pH decreases following meals in general and the rate of decrease in rumen pH is high when the meal is large (Krause and Oetzel, 2006). This is explained by the reduced salivary secretion when dairy cows ingest a large meal in a short time, resulting in a decrease in the buffering capacity of the rumen and a consequent depression in the rumen pH (Beauchemin et al., 2008). In contrast, maximizing the buffering capacity of the rumen and lowering the episodes of low rumen pH can be

### Table 1
Estimations of the amounts of physically effective fiber inclusive of particle > 1.18 mm (peNDF$_{1.18}$, % of DM) recommended in the diet of dairy cows with varying contents of ruminally degradable starch (RDS) from grains and dry matter intake (DMI). Adapted from GfE (2014).

<table>
<thead>
<tr>
<th>RDS from grains (% of DM)</th>
<th>DMI (kg/d)</th>
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<td>18</td>
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<tr>
<td>8</td>
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<td>16</td>
<td>25</td>
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<td>20</td>
<td>32</td>
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</table>

The recommendation was derived using a ruminal pH value of 6.2 with the following equation:

\[
\text{ruminul pH} = 6.05 + 0.044 \times X_1 - 0.0006 \times X_1^2 - 0.017 \times X_2 - 0.016 \times X_3
\]

where:
- \(X_1 = \text{peNDF}_{1.18}\) (% of DM), \(X_2 = \text{RDS from grains in the diet (% of DM)}, X_3 = \text{DMI (kg/d); root mean square error = 0.11, } R^2 = 0.66\) and \(P < 0.001\) (Zebeli et al., 2008).
- \(\text{peNDF}_{1.18}\) contents of greater than 32% may limit DMI potential of the cows, so that the expected DMI level may not be reached.

### Table 2
Estimations of the amounts of physically effective fiber inclusive of particle > 8 mm (peNDF$_{8}$, % of DM) recommended in the diet of dairy cows with varying amounts of total starch and dry matter intake (DMI).

Adapted from GfE (2014).

<table>
<thead>
<tr>
<th>Total starch (% of DM)</th>
<th>DMI (kg/d)</th>
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<td>18</td>
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</table>

The recommendation was derived using a ruminal pH value of 6.2 based on the following equation:

\[
\text{ruminul pH} = 6.19 + 0.0438 \times X_1 - 0.000847 \times X_1^2 - 0.000288 \times X_2 - 0.001341 \times X_3
\]

where:
- \(X_1 = \text{peNDF}_8\) (% of DM), \(X_2 = \text{total starch content in the diet (% of DM)}, X_3 = \text{DMI (kg/day); root mean square error = 0.11, } R^2 = 0.65, P < 0.001\) (Zebeli et al., 2010c).
- \(\text{peNDF}_8\) contents of greater than 18% may limit DMI potential of cows, so that the expected DMI level may not be reached.
obtained when dairy cows consume their diet slowly and more frequent and in small meals during the day. Carter et al. (1990) observed linear increase in total saliva production with increasing feeding frequency, whereby an increased frequency from one to eight meals led to a 34% increase in total saliva production. Nevertheless, Oetzel and Nordlund (1998) pointed out, that increasing the frequency of feeding (e.g., six times vs. twice daily) might decrease the variation in post-feeding ruminal pH, but can also lead to increased DMI, thus resulting in lower mean ruminal pH. However, chewing during rumination stimulates secretion of bicarbonate-rich saliva, which together with the reflux of bicarbonate due to exchange of SCFA helps in buffering the rumen and regulation of rumen pH and proper fermentation (Fig. 1).

Although feeding of TMR aims to ensure adequate ingestion of peNDF and minimize the selective consumption of grains or fine particles (sorting behavior), sorting of TMR and discrimination against longer forages can result in less peNDF and high RDS ingested by dairy cows, thus increasing the risk of rumen disorders (Leonardi and Armentano, 2003; DeVries et al., 2008). Thus, during transition and early lactation, not only diet composition per se, but also feeding management such as minimization of sorting behavior of the cows through distribution of the TMR more frequently, providing sufficient eating space, avoiding stress and adequate mixing of the feed need to receive particular attention.

Failure to guarantee a smooth adaptation of the rumen and to formulate best quality, hygienic (i.e., roughages, silage and concentrates with mycotoxin contaminations) and balanced ration (i.e., inadequate amounts of the required nutrients, insufficient amounts of peNDF coupled with excessive levels of RDS; Tables 1 and 2), as well as inappropriate feeding management lower ruminal pH, increase the odds of rumen metabolic disorders during early lactation. In addition, there is evidence that cows during the transition period reduce their rumination activity (Calamari et al., 2014). The latter authors suggested monitoring rumination activity around calving and in particular during the first week of lactation, as a way to identify cows at a greater risk of developing rumen disorders in early lactation. Especially cows with a slower increase in rumination time after calving are at greater risk of inflammation and clinical diseases in early lactation as observed by Calamari et al. (2014). Thereof, rumination time could be used as an index of the welfare of the herd, although it has to be emphasized that no absolute value can be stated, as the average rumination time is influenced by several factors. Thus, further research is warranted to define the threshold of rumination time in different feeding systems and under different climatic and management conditions (Calamari et al., 2014). In this context, we have recently observed rapid depression of ruminal pH around calving in a periparturient dairy cow (Fig. 2). In this cow, rumen pH and temperature were monitored every 10 min using wireless sensors during the entire period around calving. Ruminal pH dropped following a sigmoidal shape from approximately 6.4 to below 5.8 for the major part of the day, starting 5–6 days before the parturition day. The threshold of pH 5.8 is often used as an indicator of SARA in dairy cows (Zebeli et al., 2008), suggesting an increased risk of SARA around calving. The episodes of pH drops were more apparent during daylight hours (08 am–6 pm) than at night especially after calving. These data support those of Calamari et al. (2014) and appear to suggest not only a reduction in rumination activity but also exceeding the capacity for pH regulation (refer to Fig. 1) around parturition in dairy cows.

In addition, SARA susceptibility may also be affected by the lactation number of cows. In general, the effect of parity on the risk of developing SARA has not been described in detail and contradictory observations have been reported previously (Maekawa et al., 2002; Bramley et al., 2008). Nevertheless, one could assume that primiparous cows should be at lower risk for SARA due to their lower DMI and also lower production level. However, we have recently observed contrary results, showing longer times in which the pH dropped below a threshold of pH 5.8 (25 min/d) and pH 6.0 (66 min/d) in primiparous cows compared to cows in second or higher lactation (Humer et al., 2015). The reason for a possible exacerbation of the occurrence of SARA in first production heifers might be that these cows have not had previous long-term exposure to a highly fermentable lactation diet. Thus, they may have fewer rumen papillae and different microbial community profiles than mature cows (Penner et al., 2007; Bramley et al., 2008). Accordingly, it is assumed that heifers need time to self-regulate their own ruminal pH after they start consuming large amounts of cereal grains after parturition (Oetzel, 2007). Therefore, it is of special importance to optimize the feeding and management (i.e., providing sufficient amounts of peNDF, avoiding excessive amounts of RDS, ensuring hygienic feeds and homogenization of the diets to counteract sorting in favor of fine particles, providing sufficient eating space and avoiding stress), as well as the monitoring (e.g., monitoring of the rumination time) of primiparous cows in the peripartal period to prevent SARA conditions.

2.3. Body condition management and protein feeding postpartum and fertility

With regard to fertility, excessive NEB in early lactating cows was shown to delay the recovery of the uterus, reduce ovarian function and the early embryo development (Butler and Smith, 1989; Butler, 2003; Wathes et al., 2007), in addition to the reduction in the expression of estrous (Diskin et al., 2003). The degree of NEB can be monitored by BCS which gives an indirect measure for tissue reserves and their mobilization (Schröder and Staufenbiel, 2006). Body condition is typically scored on a scale from 1 to 5 where 1 is emaciated and 5 is extremely fat (Schröder and Staufenbiel, 2006). Reduced reproductive performance has been related to low BCS at the first insemination (Ferguson, 2002). Similarly, lower BCS is associated with a delay in the first ovulation in dairy cows at 5–11 weeks after calving (Shrestha et al., 2005). A study conducted by our group (Fig. 3) showed that the likelihood of successful conception measured until 17 week postpartum increases with the increase in the BCS of the cows postpartum (Fig. 3A). Increasing BCS from 2.5 to 3.0 at the peak of lactation (6 to 8 weeks of lactation) increases the likelihood of successful conception from below 25% to above 50% in cows until the week 17 postpartum (Fig. 3A). The same study suggested that meeting the requirements of early lactating cow (until 4 weeks postpartum) with utilisable protein in duodenum (uPD) is also instrumental for improving conception rate of the cows (Fig. 3B). For example, increasing the intake of uPD early postpartum from 90 to 110% of theoretical requirements can improve conception rate from 25 to 75%. A 650-kg body weight cow producing 45 kg milk/d with 4% fat and 3.3% protein requires at the peak of lactation approximately 180 MJ NEL and 4.3 kg of uPD per day (GIE, 2001). Because of the limited DMI level, cows typically experience a deficit both in energy and uPD during this period, which is expected to be deeper during SARA. Per definition, uPD is the protein being absorbable at the
duodenum and consists of microbial protein plus ruminally undegradable protein (UDP) (GfE, 2001). Because of high requirements in uPD and limitation in the capacity of microbial protein synthesis in the rumen (approximately 10.1 g/Mj ME ingested), diets of early lactating dairy cows need also containing sufficient protein ingredients with high UDP content. Indeed, rather than the amount, the quality of protein and promotion of DMI are critical during early lactation both in terms of production and reproduction (Butler, 2005; Drackley and Cardoso, 2014). Typically, soybean meal, fishmeal and other commercially manufactured protein sources with high UDP contents are indispensable in the diet during this period. On the other hand, high content of ruminally degradable protein (RDP) leads to elevated levels of ammonia concentration in the rumen and urea in blood, which may damage liver metabolic activity, uterine environment, and may impair fertility (Butler, 2005; Rhoads et al., 2006). Therefore, in terms of affecting fertility, the source of protein and the ratio between RDP and UDP in the diet, and the amount of uPD absorbable at duodenum are more important to take into account in diet formulations than the content of crude protein in the diet of early lactation dairy cows.

3. Rumen health status and its implications in overall health and fertility

3.1. Impacts of rumen disorders on systemic inflammation

Rumen metabolic disorders are associated with accumulation of excessive amounts of SCFA and potentially lactate in the rumen fluid, which are responsible for lowering the rumen pH and a consequent impairment of the acid–base balance (Nagaraja and Titgemeyer, 2007). Dysfermentation and dysbiosis in the rumen are main features of rumen disorders such as SARA, which has been extensively elucidated during the last few years (Khaipour et al., 2009; Ametaj et al., 2010b; Saleem et al., 2012; Petri et al., 2013). A vast amount of research has shown that dysbiosis leads to the initiation of a chain of metabolic alterations in the rumen and other parts of the gastrointestinal tract (Li et al., 2012; Plaizier et al., 2012; Metzler-Zebeli et al., 2013), which may result in the release of large amounts of multiple microbe-derived toxic compounds in the lumen of the gastrointestinal tract (Zebeli and Metzler-Zebeli, 2012). Of these toxic compounds generated in the rumen during dysbiosis, cell-free lipopolysaccharides (LPS) or commonly known as endotoxins, as well as enterotoxins have been associated with many systemic diseases in ruminants (Ametaj et al., 2010a; Plaizier et al., 2008, 2012). The presence of local gut inflammation results in the disruption of the epithelium lining of the gastrointestinal tract in the terms of alterations in the tight junction proteins and higher permeability of gut epithelium leading to entrance of these luminal toxins into the blood circulation (Steele et al., 2011; Zebeli and Metzler-Zebeli, 2012; Hollmann et al., 2013). Following the presence of microbial-derived toxins, the first responders, local macrophages, secrete a large array of pro-inflammatory cytokines, which is perceived as a low-degree inflammation in cows during SARA (Zebeli and Metzler-Zebeli, 2012; Plaizier et al., 2012). In this context, Zebeli et al. (2012b) used a meta-analysis approach to characterize the effects of diet on systemic inflammation in dairy cows. The latter authors described positive correlation between the level of concentrate in the diet, especially starting from 45% concentrate in the diet, and serum amyloid A (SAA), which is an acute phase protein and an inflammatory marker used in cattle studies (Plaizier et al., 2012).

3.2. Impact of rumen health and oxidative stress on metabolic health: the link to fertility

Activation of the innate immune response with higher levels of cytokines and acute phase proteins in blood is a hallmark of inflammation associated rumen digestive disorders (Plaizier et al., 2008; Zebeli and Metzler-Zebeli, 2012). The mechanisms of the activation of this type of inflammation seem to be identical with other common inflammatory processes in cattle which start with stimulation of Toll-like receptor (TLR)-4 cascade, activation of the transcriptional pathways and the subsequent release of pro-inflammatory cytokines (Claudio et al., 2013; Ringseis et al., 2015). Inflammation has commonly been observed during the transition period in cows (Ametaj et al., 2005; Røntved et al., 2005; Karcher et al., 2008; Catalaní et al., 2010; Gessner et al., 2013; Graugnard et al., 2013; Farney et al., 2013); however, its underlying mechanisms and clinical relevance have not yet been elucidated (Bradford et al., 2015). Potential causes of inflammation have been associated with the increased risk to develop SARA during the transition period as well as with the greater odds of transition cows to develop infectious diseases such as mastitis, metritis or laminitis (Ametaj et al., 2010a; Ringseis et al., 2015).

Systemic inflammation together with shifts in the metabolic acid-base balance during SARA as well as high levels of circulating reactive oxygen species (ROS) directly after calving are severely harmful for the host cow during the transition period. The ROS are free radicals characterized by the presence of at least one unpaired set of electron in their membranes which are highly susceptible to oxidative stress (Spears and Weiss, 2008). Previous studies have documented that transition cows typically undergo oxidative stress (Bernabucci et al., 2005; Sordillo and Aitken, 2009; Sordillo et al., 2009), whereas some evidence indicates increased oxidative stress in cows following SARA (Guo et al., 2013), probably due to systemic inflammation. A recent review by Ringseis et al. (2015) suggested that oxidative stress of the liver cells can activate the nuclear factor kappa receptor (NF-κR)}
which triggers inflammation. On the other hand, inflammation stimulates the production of ROS, triggering an aggressive cycle of responses. It is therefore not surprising that the levels of antioxidants circulating in the blood are very low during the transition period in dairy cows (Calderon et al., 2007). Moreover, antioxidants are severely reduced during mastitis and other infectious diseases associated with the transition period of dairy cows (Rezamand et al., 2007). In particular, vitamin E and selenium are essential micro-nutrients that are highly important as antioxidants. Thus, the National Research Council (2001) recommends extra supplementation of vitamin E during periods of immune suppression, such as around calving, as the vitamin E status of the cow is one important component of a well-functioning immune system (Kaflizadeh et al., 2014). As antioxidants are necessary to prevent reproductive disorders, several studies investigated the effects of vitamin E, Se or their combination, reporting either no effect (Gunter et al., 2003) or an increase in fertility (Segerson et al., 1981; Aréchiga et al., 1994).

Another important etiological factor suggested to link inflammation with metabolic health during the transition period with consequences for fertility is that inflammation is involved in the development of fatty liver syndrome (Ametaj et al., 2005; Bradford et al., 2009; Ringseis et al., 2015), which largely impairs hepatic metabolic activity. Accumulation of fat in the liver is known to impair fertility in cows (Rukkwamsuk et al., 1999). Specifically, it has been suggested that accumulation of the fat in the liver can reduce the ability of hepatocytes to metabolize or clear the reproductive hormones (Reynolds et al., 2003) and consequently modulates the signals to reproductive organs and pituitary gland. In addition, there is a mechanistic link suggested between disturbances in lipid metabolism and immunity, whereby excessive NEFA or ketonemia can down-regulate immune responses in dairy cows (Wood et al., 2009; Zarrin et al., 2014).

Direct negative effects of SARA on metabolic disturbances (Zebeli et al., 2010b, 2011) and liver functions were also reported (Loor et al., 2007; Drackley and Cardoso, 2014), and apoptosis of hepatocytes of cows during SARA in the early lactation (Loor et al., 2007; Tharwat et al., 2012). During periods of such excessive stress, dairy cows direct some of the available net energy and nutrients to overcome cellular damage, immunological stress, and metabolic disturbances (Esposito et al., 2014), at the expense of productive and reproductive processes (Khiaosa-ard and Zebeli, 2014). Although in cattle, and in particular in dairy cattle, more experimental data are needed to make an association between immune activation and energy and nutrient expenditure, loss of energy and nutrients during immune activation and stress-related processes could represent a major obstacle for efficient productivity (Zebeli and Metzler-Zebeli, 2012). All of these metabolic factors associated with SARA and metabolic health can either directly or indirectly impair fertility and are depicted in Fig. 4.

Rumen disorders and inflammation are typically associated with reduced DMI (Plaizier et al., 2008), aggravating further the NEB of cows during early lactation. The energy which is required for normal homeostasis during the early lactation period might be used at the expense of energy and nutrients needed to support reproductive performance and milk production. Because homeorhetic regulation directs the energy and nutrients for milk production rather than for reproduction, fertility

Fig. 4. Graphical presentation of the interrelationships among unbalanced diet and resulting rumen and systemic disorders during transition period and their effects on fertility of cows: RDS, rumen degradable starch; pNDF, physical effective neutral detergent fiber; SCFA, short-chain fatty acids; NEB, negative energy balance; NEFA, non-esterified fatty acids; DMI, dry matter intake; BHBA, beta-hydroxy-butyrate; BCS, body condition score; ROS, reactive oxygen species; IL-1, interleukin 1; IL-6, interleukin 6; COX, Cyclooxygenase; APP, acute phase proteins; GnRH, gonadotropin-releasing hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; PGF₂α, prostaglandin F₂α; P₄, progesterone and E₂, estradiol; endotoxin.
is the parameter suffering most from such metabolic alterations (Drackley and Cardoso, 2014). The lowered DMI decreases supply to the liver of key nutrients including glucose, amino acids, and also SCFA particularly propionate is required for gluconeogenesis (Fig. 1). Furthermore, muscle protein mobilization with utilization of glucogenic amino acids as energy source starts before fat mobilization at times around calving which leads to loss of muscle mass. The decrease in metabolizable protein or uPD due to insufficient DMI in early lactation may be linked to ketosis and other peripartal diseases, which in turn may decrease fertility (Van der Drift et al., 2012; Roche et al., 2013; Drackley and Cardoso, 2014), as indicated in Fig. 3b. Thus, lower levels of nutrients available for reproduction together with a NEB during early lactation, which can be aggravated by SARA and related disturbances, play a significant role in infertility of high-producing dairy cows.

In fact, during the period of excessive NEB, the reproductive performance is adversely affected, partly at least because it decreases the release of luteinizing hormone (LH), estrogen and progesterone concentrations, and growth of follicles and corpus luteum (Butler, 2003; Garnsworthy et al., 2008). Moreover, insulin concentration that reflects the net energy available and dietary sufficiency is suggested to be a key parameter linking the metabolic health with the reproductive performance (Drackley and Cardoso, 2014). Insulin strongly decreases shortly before parturition and increases later postpartum (Grum et al., 1996). It is known that insulin is required for synthesis of insulin-like growth factor-I (IGF-1) in the hepatocytes in response to the higher level of growth hormone (somatotropin) resulting in production of estradiol in higher amounts from dominant follicles, more LH receptors for ovulation and development and growth of corpus luteum (Lucy, 2000; Garnsworthy et al., 2008; Drackley and Cardoso, 2014). Thus, lower insulin and IGF-1 during NEB in early lactating cows can occur during first ovulation, first estrus and conception leading to decreasing fertility in terms of reduced conception rate and pregnancy (Drackley and Cardoso, 2014).

3.3. Early embryo failure in cows

In order to better understand the link between rumen health, overall health in early lactation cows and fertility, the mechanisms behind early embryo failure are highlighted in this section. In dairy industries the last decades were characterized by an intensive selection of cows for milk yield which has been associated by a declining trend of reproductive performance. This decline of reproductive success became a major constraint in the reproductive management of dairy herds. Meanwhile it has been approved that traits such as poor expression of estrus (behavior and duration, ovulation rate), metabolic disorders and increase of diseases (susceptibility to infections such as endometritis, lameness, mastitis) have negatively affected fertility (Lopez et al., 2004). It is generally accepted that successful implantation depends on the quality of the embryo, a receptive uterine environment and the embryo–maternal synchrony as a prerequisite for an optimal crosstalk between the conceptus and the endometrium (Lucy et al., 2014). The key to this process is dynamic and precisely controlled molecular and cellular events that drive implantation and establishment of pregnancy (Thatcher et al., 2001).

One of the major obstacles of fertility in dairy cows is during early embryogenesis. In dairy cows, although natural mating or artificial insemination results in high rates of fertilization, the percentage of calving is rather low which indicates a drastic loss of embryos and/or fetuses (Lucy et al., 2014). It is well accepted that a major part of these losses occur during early embryo development. Diskin et al. (2006) showed that there is a clear tendency of an increase of early embryo death. In 1980, early embryo death in British Friesian cows reached about 28%, whereas 26 years later already 43% of inseminated Holstein-Friesian cows lost the embryo during the early developmental stage (Diskin et al., 2006). Moreover, it was shown that a very high proportion of embryos do not survive beyond day 7 (Diskin et al., 2006) or at least between days 8 and 17 of pregnancy suggesting that early embryonic mortality is the main source of reproductive wastage (Thatcher et al., 2001; Humblot, 2001; Fazeli, 2008). Meanwhile several studies have been performed in order to get more information about the fate of these embryos. For example, in vitro derived embryos have been transferred either into heifers, on day 2 of the estrous cycle, or in dairy cows, 60 days post-partum, or in dried cows, and re-collected after 7 days. It was demonstrated that the reproductive tract of milking cows, which showed deviation of common metabolic parameters such as greater NEFA and BHBA as well as lower glucose, insulin, and IGF-1, is compromised in its ability to support early embryo development compared with cows dried off and heifers, as fewer embryos developed to the blastocyst stage in lactating cows compared to non-lactating dairy cows (Maillo et al., 2012; Rizos et al., 2010).

Considerable discussions are ongoing on the impact of fetal programming on subsequent progeny performance, with most research being undertaken using epidemiological data. For example, Berry et al. (2008) used large epidemiological data of dairy cattle in Ireland and concluded that prenatal factors affect the subsequent performance and health of the offspring. Regression analyses of maternal mixed model solutions on dam milk production at different stages relative to conception revealed that greater milk yield of the dam during preconception and gestation was associated with reduced survival and greater somatic cell count in the progeny, suggesting that offspring survival and performance are affected by prepartum conditions that offsprings experience as an oocyte, embryo, or fetus. However, this analysis could not explain how the impaired fertility is mediated through high milk production (or factors related to high milk production) of the dam (Berry et al., 2008), which does not provide direct evidence of a link between high milk production potential with low fertility of the cow. Although the possibility of epigenetic modifications to the genome during the early postpartum period that affect long-term developmental competence of follicular cells has not yet been clearly demonstrated, there are suggestions that it is only possible to correct the epigenetic metabolic programming of the imprinted cells (in this case the oocyte, granulosa and theca cells), when they run through their physiologically relevant life span. As bovine follicles require at least 60 to 80 days to fully develop, low conception rates may be caused even more by conditions that consisted at times long before insemination than on the period immediately preceding insemination. Hence, it seems to be of utmost importance that cows experience no adverse metabolic conditions in early lactation (Britt, 1991; Lucy et al., 2014). Again, the way to do so is to guarantee a smooth transition of the cow.

3.4. Impact of systemic inflammation and stress on fertility

Immune stress inhibits reproductive functions and thus impairs fertility (Hansen et al., 2004). In a recent study, Ametaj et al. (2014) demonstrated that intravaginal administration of probiotics in periparturient cows lowered systemic inflammation and enhanced both performance and fertility in dairy cows. On the contrary, administration of endotoxin or its related inflammatory markers such as cytokines have been shown to negatively impact fertility. For example, endotoxin administration inhibited pulsatile LH secretion in many species including cattle (Peter et al., 1989), and delayed or completely blocked the preovulatory LH surge (Suzuki et al., 2001). Cytokines such as interferon (INF)-β decreased the secretion of LH (McCann et al., 2000) which resulted in suboptimal luteal function, absence of ovulation and compromised follicle and oocyte development (Chebel, 2007). Furthermore, cytokines have direct adverse effects on the ovary. For example, interleukin (IL)-6 inhibits the estradiol secretion and consequently reduces LH secretion (Alpizar and Spencer, 1994). Other cytokines like tumor-necrosis factor (TNF)-α and INF-α caused cytotoxicity in the corpus luteum and reduced the progesterone secretion (Fairchild and Pate, 1991; Petroff et al., 2001). Moreover, TNF-α was found to be a key factor inhibiting the process of oocyte maturation.
and induces embryo apoptosis (Soto et al., 2003). Cytokines such as TNF-α and IL-1β caused an elevation in the secretion of prostaglandin F2α (PGF2α), a disruptive molecule to oocyte and embryo, which induces luteolysis and inhibits the oocyte maturation and embryonic development (Fazio et al., 1997; Soto et al., 2003; Hansen et al., 2004).

In recent studies conducted with anestrous ewes, it was shown that suppressive effects of endotoxin on reproduction occurs primarily at hypothalamic level, changing the gonadotropin-releasing hormone (GnRH) synthesis and release, and at the pituitary level by inhibiting release of LH from gonadotropic cells (Haziak et al., 2014). Preliminary results of Williams et al. (2011) indicated that the preimplantation embryo is sensitive to maternal systemic inflammation, with effects on blastocyst cell lineage allocation, and even consequences for behavior and health in adult offspring in rodent models. The latter findings were described in mice models; however, they suggest potential involvement of systemic inflammation in infertility and subsequent health status of the offspring. Because the risk of inflammation during early lactation is high in dairy cows both due to infectious diseases like endometritis, mastitis but also in response to SARA, laminitis and potential surgery such as displacement of abomasum, it is possible that the same events are true for dairy cows as well.

Although there are no reports available to directly link or not the SARA-induced inflammation to infertility, the link between udder inflammation such as mastitis and infertility has been reported many years ago (Hansen et al., 2004). It was shown that mastitis is associated with altering the development of ovarian follicle in dairy cattle (Rahman et al., 2012) with a negative impact on the reproductive efficiency (Schrick et al., 2001). A recent report by Dong et al. (2014) demonstrates that feeding high concentrate diets to dairy cows resulted in epigenetic changes, as shown by reduced histone H3 acetylation and altered methylation of specific genes involved in fat and protein synthesis in the mammary gland (i.e., reduced methylation of the gene encoding the signal transducer and activator of transcription 5A and increased methylation of the stearyl-coenzyme A desaturase gene), possibly due to higher release of LPS to mammary blood. In this context, pro-inflammatory cytokines produced either during SARA and during mastitis can lead to liver damage and can negatively affect the hypothalamic pituitary ovarian axis and reduce the fertility of cows (Hansen et al., 2004).

It is widely accepted that exposure of cows to LPS leads to a higher level of circulating cortisol, a stress hormone that blocks the secretion of LH, thereby impairing the ovulation and follicle development (Padmanabhan et al., 1983; Chebel, 2007). Besides inflammation, increased concentrations of cortisol are also common findings during SARA and feeding of high grain diets to dairy cows (Dong et al., 2013; Jia et al., 2014). Although the research is far from establishing a causal relationship between cortisol levels and long term fertility in cows, this potential association still suggests an additional mode of action of rumen disorders and SARA to adversely affect fertility in cows.

4. Conclusion

Overall, rumen disorders are multifaceted nature because they do not only affect rumen health and proper digestion but also general health, metabolic health, performance and fertility of cows. From the perspective of preparing the cow for a successful reproduction, enhancing rumen health becomes particularly important during the transition period. On the one hand, transition cows are highly dependent on energy output generated in the rumen. Also, these cows are highly sensitive to environmental changes, whereby a healthy rumen supports overall health with positive implications for fertility, and vice versa. Feeding management during transition period should target rumen health and lowering systemic inflammation as proactive strategy to enhance health and reproductive performance in dairy cows.

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