An update on epigenetics, metabolic programming and monitoring tools in pre-weaned dairy calves

Abstract

The current knowledge on the effects of nutritional and environmental factors in the late embryonic and neonatal phase of dairy calves on performance later in life is summarised. The importance of epigenetic factors are increasingly recognised in this context.

Prolonged colostrum feeding, discouraged on most farms to prevent the spread of Johne's disease, can have beneficial effects on the calf's immune system and has been shown to give protection against rotavirus. The importance of colostrum hygiene for uptake of antibodies is explained.

Intensive milk or milk replacer feeding leads to a more productive animal while reducing the rearing costs.

Iron deficiency anaemia is a common condition in whole milk fed dairy calves, and monitoring haemoglobin and supplementing iron where necessary leads to higher growth rates in calves.

Other monitoring tools like lung ultrasound, beta-hydroxy-butyrate at weaning are briefly introduced.

In conclusion the benefits of many early intervention measures are likely to be underestimated.

Introduction

On UK dairy farms youngstock rearing is the second biggest cost factor after feed costs, and on many farms there are many opportunities to improve welfare and profitability. This article summarises some of the relevant recent research on factors which influence early development with long lasting effects, and gives an overview about available calf health monitoring tools.

Metabolic programming, epigenetics, early influences on development

Epigenetics describes influences on and effects of differences in gene expression. DNA contains a code made out of genes which encode proteins/enzymes. Proteins are produced in the processes of transcription (production of RNA out of DNA) and translation (production of chains of amino acids based on the RNA sequence in the ribosomes). The DNA sequence is fixed and identical in every cell. However, transcription can occur at variable efficiency, and many steps from the DNA to the protein are dependent on environmental factors. E.g. methylation can silence areas of the DNA, and other mechanisms affecting gene expression are known (e.g. histone modification, non-coding RNA, (Chavatte-Palmer et al. 2018) but are beyond the scope of this article. Epigenetic effects are mostly relevant in the embryonic and neonatal stage, and they can be passed on over more than one generation via the maternal or paternal side, with the latter having been overlooked for many years.

Epigenetic effects were first observed and researched in humans, for example in studies on children and grandchildren of malnourished parents during periods of famine and war in the Netherlands (Heijmans et al. 2008). They are now linked to aspects of conditions like obesity and coronary heart disease (Gluckman and Hanson 2004).

Some examples of early metabolic and epigenetic effects in animals are:

- A high fat diet fed to **male** rats produced β cell dysfunction in female offspring with change in glucose metabolism and increased obesity (Ng et al. 2010)
- Heat stress in dry cows reduced first lactation milk yield in daughters by 2.2 kg/day, with increased culling before first calving and a reduced productive lifespan. In the **granddaughters** of heat stressed cows milk yield per day was still reduced by 1.3 kg/day, with increased culling before first calving but no reduction in productive lifespan (Laporta et al. 2020)
- Skibiel *et al.*, (2018) examined the mechanisms behind the effect of heat stress and found smaller alveoli in the mammary glands in heifers out of heat stressed cows and different methylation profiles of liver and mammary DNA which may explain the differences in morphology

- Ling *et al.*, (2018) found different markers for immune function in calves out of cows who suffered metabolic stress in late pregnancy.
- Martin *et al.*, (2007) compared replacement beef suckler heifer calves out of cows which were protein supplemented in late gestation with calves out of unsupplemented cows. Calves out of supplemented cows showed similar birth weights, higher weights pre-breeding, similar age at puberty, higher pregnancy rates and higher percentage calving in the first three weeks of their first calving season.
- Mossa *et al.*, (2013) found a lower ovarian follicular reserve in calves out of cows which were undernourished during pregnancy.
- Soberon *et al.*, (2012) compared nutrient intakes from milk replacer pre-weaning, growth rates and first lactation yield in dairy heifers in two herds. For the two herds he found that for every kg of pre-weaning daily liveweight gain (DLWG) fist lactation yield increased by 850 and 1113 kg.
- Brown *et al.*, (2005) found more mammary cells and more active metabolism in heifers with high pre-weaning energy and protein intake. This partly may explain the higher first lactation milk yields in calves fed intensive milk diets.

This beneficial effect of intensive/increased milk intake in pre-weaned calves has been confirmed in many other studies and combines a higher feed efficiency and therefore reduced overall rearing costs with a higher quality production animal as a result. The reluctance of some farmers to increase milk allowance in order to save money often is irrational: Hawkins *et al.*, (2019) concluded in a comparison that per kg of daily liveweight gain (DLWG) intensively reared calves had the lowest feed costs, which is due to a reduced number of days the calves require feeding for maintenance.

These mostly hidden effects of epigenetic mechanisms make it difficult to run accurate cost-benefit analyses of intervention measures. Considering the known long term effects of early environmental and nutritional factors it is very likely that the benefits of improving those factors are commonly underestimated. Laporta *et al.*, (2020) in their heat stress study estimate the total milk loss in cows' daughters in the US due to heat stress as $ 371 Million ($ 39 per daughter per year). This did not include effects on the cows themselves, the granddaughters and other factors than milk yield.

In the UK the practical implication is especially prominent in autumn calving herds spending the dry period outside in the summer. The provision of shade for these cows must be a priority.

Colostrum and transition milk

The importance of colostrum feeding is well known, and there is no need to repeat general knowledge. Raboisson *et al.*, (2016) carried out a meta-analysis on failure of passive transfer (FPT) and concluded that affected calves have an increased risk of mortality by a factor of 2.16, of respiratory disease of 1.75 and of diarrhoea of 1.51. They calculated the mean cost of FPT in dairy calves as € 60. Considering that the main input of improved colostrum management is time it is obvious that even with a modest reduction in FPT this time invested will be well paid.

Monitoring of serum protein as a proxy for antibody uptake in the first 7-10 days with a refractometer is commonly carried out, and if the uptake is insufficient in a proportion of calves the three Q's (quality, quantity, quickly) are followed up, including quality assessment with a Brix refractometer. However a fourth factor is known but often overlooked in practice – hygiene. It is well established that pasteurisation leads to higher, not lower uptake of antibodies by the calf (Gelsinger et al. 2014). Therefore, on farms with FPT colostrum hygiene should be an area of closer examination. McGuirk and Collins, (2004) recommend a total bacterial count of less than 100,000 cfu/ml and a faecal coliform count of less than 10,000 cfu/ml. These can be monitored using commercial labs or on dairies or vet practices using simple kits like Petrifilm™ (Fig 1).

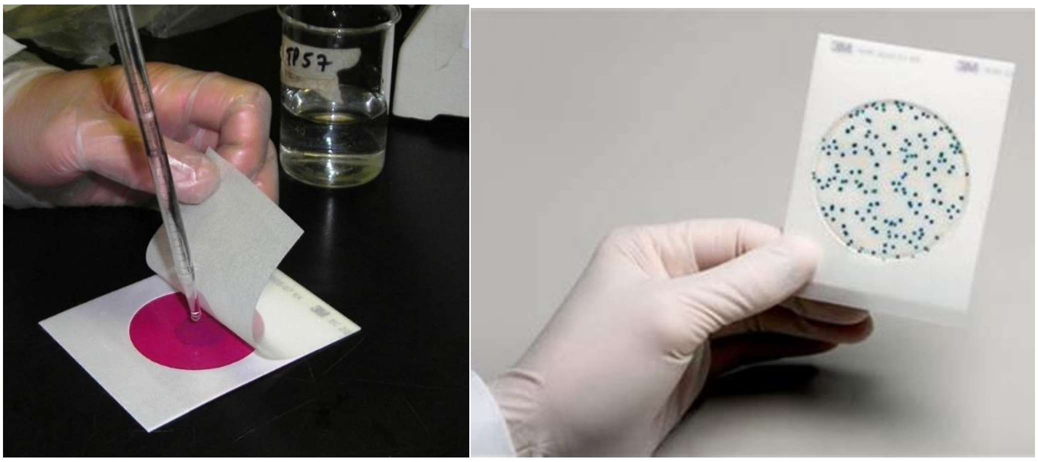

Fig 1: Petrifilm inoculation and reading

Since Johne’s disease control became widespread a common policy is to feed colostrum only on day 1 and then switch to milk replacer. However, Kargar *et al.*, (2020) compared the effects of short term and extended colostrum feeding on the performance of calves. All calves were fed 5 litres daily for 14 days, one group milk only, one group 4.650 l of milk and 0.350 l of colostrum and one group 4.3 l of milk and 0.7 litres of colostrum. Prolonged partial colostrum feeding lead to higher weight gains and less days with high temperatures. It is postulated that factors in colostrum (e.g. insulin and insulin-like growth factor-1) may stimulate intestinal development.

Earlier (Parreño et al. 2010) found that supplementing milk with colostrum for 14 days gave effective protection against rotavirus.

Therefore, on farms where calf health is a more prominent issue than Johne’s disease, a balance should be reached between Johne’s control and improved calf health. Extended feeding of hygienically harvested and possibly pasteurised colostrum over a longer period may re-gain its place on some farms. Before Johne’s disease became a recognised issue this was a widespread practice.

Iron status of wholemilk fed calves

Iron deficiency anaemia is a well-recognised condition in pigs, but unlike in some other countries less recognised in calves in the UK. Calves are born with a limited reserve of iron, and whole milk only contains a small proportion of the calf's iron requirement and very small amounts of trace elements in general. As in pigs, outdoor reared calves may receive iron from the soil, but indoor reared calves do not have access to any natural iron. Work in the 1980s showed decreased rates of diarrhoea and pneumonia in iron-supplemented calves (Bünger *et al.*, 1986). Allan *et al.*, (2020) carried out a study on over 200 calves in the south of England and showed an average increase in DLWG in the first six weeks of 78 grams/day in calves injected with 1 gram iron as iron dextran in the first 10 days of life. 34 % of untreated calves had a haemoglobin level below 9 g/dl at six weeks of age. Therefore, iron deficiency anaemia is widespread in whole milk fed calves, which includes organic dairies and many other low input systems. In the UK there are currently no iron supplementation products licensed for calves. Iron is not only part of haemoglobin but also an important part of anti-oxidants and plays a direct role in several immune functions, e.g. leads to increased phagocytic activity in monocytes and stimulates the production of cytokines.

Haemoglobin levels at four to six weeks are a good indicator to assess the status, or alternatively iron could be supplemented in some calves and health and growth rates compared. There is also a point of care test available AniPoc™, which in a small study showed good correlation with values from an accredited laboratory (Allan, J. and Plate, P., unpublished, Fig 2):

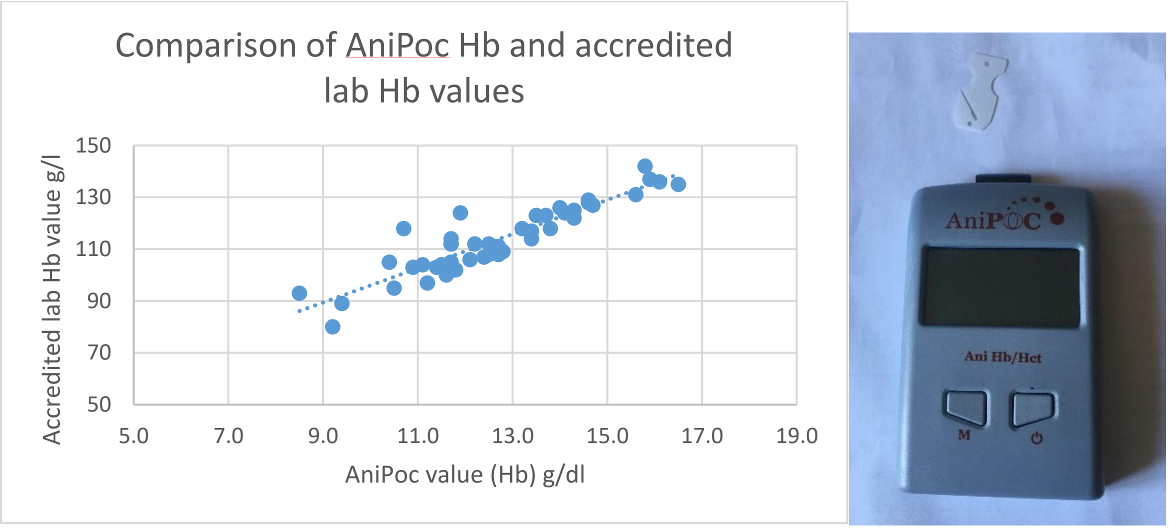

Fig 2: AniPoc™ handheld device and its performance compared with an accredited laboratory

Weaning

Traditionally calves should be weaned when they consume at least 1 kg of concentrate. Impaired rumen development around this time can lead to a reduction in DLWG and digestive problems. On farms with group housing and problems around weaning it has been shown that beta-hydroxy-butyrate is a useful indicator for rumen development, being closely correlated with butyrate in the forestomachs. Therefore in practice the glucometers used to diagnose ketosis in cows can also be used to assess rumen development in calves, with an optimum cut off point of 0.1 mmol/l. as shown by Deelen *et al.*, (2016). If an increased sensitivity (with decreased specificity) to diagnose sufficient solid intake is required the cut off point can be increased to 0.2 mmol/l.

Whether this test has its place, is practical and necessary on many farms is up to the practitioner, but it may be an aid to make informed decisions around weaning or helps to argue a case.

Calf respiratory health and environmental monitoring

Sensor technologies

Automatic temperature detectors have been available for many years, using infrared probes and signalling alerts either by a flashing light or by notification on a smartphone. Early detection of conditions like calf pneumonia does not reduce the need for antibiotic treatment: Mahendran *et al.*, (2017) found that after initial treatment with only anti-inflammatories 75 % of affected calves needed secondary antibiotic treatment for pneumonia. However, in a small, unpublished study Angel (2018) found that calves treated early for pneumonia after temperature alerts had a reduction in DLWG of only 5 g, compared with 50-100 g from the published literature. Therefore, these technologies can minimise the effects of disease.

Temperature humidity trackers

There are several tracking devices available which store data over a period which can then be downloaded or looked at live via the cloud. They can be very useful explaining the need for additional energy, calf jackets or building modifications to reduce cold stress in calves.

Thoracic ultrasound

Teixeira, Mcart and Bicalho, (2017) found a correlation between lung consolidation at weaning, diagnosed with thoracic ultrasonography, and fertility parameters later in life. Therefore, lung ultrasound could be a tool to assess bought in calves, especially if their colostrum status is unknown.

Scoring systems

The Wisconsin calf respiratory scoring system is very popular and includes rectal temperature, cough, nasal discharge, ocular discharge and ear position McGuirk and Peek, (2014), and it is suggested to score calves twice weekly and affected calves are identified using a point system. The California scoring system works along similar parameters (Love et al. 2014).

Conclusion

Although much progress has recently been made in research and knowledge transfer/knowledge exchange there are still many opportunities for vets in farm practice to improve calf and youngstock health. The effects of improvements in the dam's and calf's environment and nutrition are only partly understood, and the increasing knowledge about epigenetic factors suggests that many benefits of improvement measures may be under-estimated. E.g. colostrum application is a once in a lifetime event with long term consequences for the animal, and failure is known to be costly. There is a growing range of monitoring tools available to assess the health and nutritional status of calves, and further diagnostic tools are in development. Some farmers are still reluctant to make the necessary investments in calf health, however, with a sound cost-benefit analysis and communication skills (like motivational interviewing) significant progress is possible. With better genetic assessment tools including genomics it is possible to reduce the number of calves kept as replacements on many farms, and if beef calves are sold off the unit at a young age all efforts could be concentrated to give these calves the best start – managing less calves better.

Key words

dairy calves – epigenetics – monitoring – metabolic programming – environment - nutrition

Key points

The performance of diary cows is dependent on environmental, genetic and epigenetic factors.
Epigenetic factors can be passed from one generation to the next.
The hidden effects of early positive intervention are likely to be underestimated.
A range of old and new monitoring tools is available to assess calf performance.

CPD questions

1. Epigenetics describes
   a) The area around the DNA
   b) Differences in gene expression due to environmental and nutritional factors
   c) The likelihood of mutations
   d) The effects of DNA outside the nucleus
   e) All of the above

2. Epigenetic effects are
   a) Only temporary and can be reversed at any time
   b) Most important at the embryonic and neonatal stage
   c) Limited to the individual
   d) Passed on through generations
   e) Cannot be passed on via the paternal side

3. Heat stress in dams in late pregnancy has
   a) Only effects on the dam
   b) Temporary effects on the daughters in early life
   c) Permanent effects on the daughters
   d) Permanent effects on granddaughters
   e) Little effects on dam or offspring

4. Increased milk intake pre-weaning leads to
   a) Higher feed costs per kg of daily live weight gain
   b) Higher feed costs per day pre weaning
   c) Lower feed costs per kg of daily live weight gain
   d) Better feed conversion efficiency
   e) Increased frequency of diarrhoea

5. Increased milk intake pre-weaning leads to
   a) Higher yield in the first lactation
   b) Lower yield in the first lactation
   c) No change in first lactation yield
   d) Higher somatic cell counts in the first lactation
   e) Lower somatic cell counts in the first lactation

6. Iron deficiency anaemia
   a) Is uncommon in dairy calves
   b) Only occurs in calves fed on milk replacer
   c) Is common in wholemilk fed calves
   d) Leads to reduced daily liveweight gain
   e) Has no effects on the calf

7. Protein supplementation in late gestation led to
   a) Oversized foetuses
   b) Higher rate of twins
   c) Better fertility in female offspring
   d) Poorer fertility in female offspring
   e) No effects on the calf

8. Prolonged feeding of colostrum
   a) May increase the spread of Johne's disease
   b) Makes the calf more prone to neonatal infections
   c) Has no effect on the calf's immunity as no antibodies reach circulation
   d) Has a protective effect against rotavirus
   e) Increases the frequency of diarrhoea

9. Colostrum pasteurization
   a) Decreases antibody uptake
   b) Increases antibody uptake
   c) Has no effect on antibody uptake
   d) Cannot practically be done on farm
   e) Is the most important measure to control Johne's disease

10. Calves should be weaned
   a) At a set time
   b) When starter intakes are at least 1 kg per day
   c) When beta-hydroxy-levels in blood are at least 0.1 mmol/l
   d) When they stop drinking milk
   e) When they start eating forage

Answers

1 b; 2 b,d; 3 c,d; 4 b,c,d; 5 a; 6 c,d; 7 c; 8 a,d; 9 b; 10 b,c

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