Milk Fever Control Principles: A Review

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Introduction

Milk fever (paresis puerperalis), the clinical manifestation of parturient hypocalcaemia, is a disease of considerable importance for dairy cow welfare and economy. Although treatment with intravenous infusion of calcium salt solutions cure most clinical cases of hypocalcaemia, such cows are later more susceptible to other metabolic and infectious diseases (Curtis et al. 1983, Curtis et al. 1984). In many countries prevention of parturient hypocalcaemia is therefore given a high priority. It has been proposed that a specific control program is relevant when the incidence of milk fever increases to above 10% among high-risk cows, i.e. cows entering third or later lactations (Radostits et al. 2000). Several milk fever control principles and control factors have been described in the literature...
within the last 50 years. For a variety of reasons only 4 of these are widely used on commercial dairy farms today. These are:

I. Oral drenching around calving with a supplement of easily absorbed calcium.

II. The feeding of acidifying rations by anionic salt supplementation during the last weeks of pregnancy.

III. Feeding low calcium rations during the last weeks of pregnancy.

IV. Prepartum administration of vitamin D, vitamin D metabolites and analogues.

Other possible but less specific control measures for the prevention of milk fever include management practices such as:

V. Dietary magnesium level control peripartum.

VI. Body condition control.

VII. Controlling dietary carbohydrate intake peripartum.

VIII. Shortening of the dry period.

IX. Prepartum milking.

X. Reduced milking in early lactation.

The purpose of this review is to give an overview of the various control principles. Three (I-III) of the most widely used control principles will be discussed in detail. The use of vitamin D administration (IV) and the less specific control measures (V-X) will be addressed more briefly in the present review, which primarily focuses on controlled studies.

I. Oral calcium drenching around calving

There are many formulations available on the European and the US market for oral calcium drenching. The majority of studies documenting their effect have been done with preparations containing easily absorbed calcium salts such as calcium chloride, providing 40-50 g of calcium per dose as a bolus, a gel, a paste or a liquid (Table 1). Most producers recommend prophylactic programmes involving 4 doses. Oral calcium drenching is also recommended as a supplement to intravenous therapy for the prevention of milk fever relapses (Table 2). In this case a programme involving 1 or 2 doses is most often recommended.

Main mechanism and effect. The principle was originally developed for therapeutic use in cows with milk fever, as an alternative to intravenous calcium infusions (Glawischnig 1962). A handful of calcium chloride was dissolved in a bucket of water and given by stomach tube. However, as discussed below, such calcium chloride drenchings were later discovered to have a prophylactic effect also, when given according to a programme covering the peak of the risk period. Oral calcium drenching should preferably provide free (ionised) calcium, because this form is most quickly absorbed from the rumen and abomasum.

Normally cows absorb calcium by 2 mechanisms: active transport across intestinal epithelial cells and passive transport between intestinal epithelial cells (Goff & Horst 1993). Passive transport is dependent on diffusion down a concentration gradient, and passive diffusion of Ca from the lumen of the gut to the extracellular fluids occurs when the luminal ionised Ca concentration exceeds 1 mM (Bronner 1987). Oral calcium treatment presumably increases luminal Ca concentration above 1 mM, favouring passive transport of Ca into the extra cellular fluids (Goff & Horst 1993). The capacity of the passive transport of Ca is in principle unlimited and independent of stimulation by 1.25-dihydroxyvitamin D. Thus, the net absorption of free Ca increases linearly with increasing luminal Ca concentrations (Breves et al. 1995). Increasing the amount and the number of drenchings with calcium compounds providing free calcium ions therefore quickly increases the amount of calcium ions absorbed into the
bloodstream. Supplying the cow with CaCl₂ salts may furthermore, due to the osmotic effect, stimulate the oesophageal groove reflex, permitting rumen bypass. The calcium solution thereby avoids dilution within the rumen, and a high concentration gradient would be obtained in the abomasum favouring passive Ca transport (Goff & Horst 1993). The calcium absorp-

| Reference               | Treatment                                      | Preventive effect on milk fever¹)                          | Comments                                                                 |
|-------------------------|------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------------------|
|                         |                                                 | (MF incidence in experimentals vs. controls, %)            |                                                                          |
| Ringarp et al., 1967    | Calcium chloride gel x 4-10 Around 40 g Ca / dose | 86% (7.7 vs. 53.2)                                         | Average effect obtained in seven separate studies. Occasional diarrhoea and loss of appetite |
| Jönsson and Pehrson,    | Calcium chloride gel x 3-4 54 g Ca / dose       | 51% (22.6 vs. 46.6)                                         | More cases of diarrhoea (17% vs. 10%)                                     |
| 1970                    |                                                 |                                                            |                                                                          |
| Simesen and Hyldgaard-Jensen, 1971 | Calcium chloride gel x 4-10 36 g Ca / dose   | 48% (25.6 vs. 48.8)                                         | More cases of milk fever >48 hours after calving among treated cows (12.8% vs. 2.4%) |
|                         |                                                 |                                                            |                                                                          |
| Pehrson et al., 1989    | Calcium chloride + calcium sulphate capsule x 4 46 g Ca / dose | 73% (14.6 vs. 54.8)                                         | No side-effects Administration of capsules eliminates the risk of aspiration |
|                         |                                                 |                                                            |                                                                          |
| Goff et al., 1996       | Calcium propionate paste x 4 37 g Ca / dose     | 42% (29 vs. 50)                                             | No effect on the incidence of milk fever in herds with low milk fever incidence |
|                         |                                                 |                                                            |                                                                          |
| Oetzel, 1996a           | Calcium chlorid + tricalcium phosphate gel x 4 54 g Ca / dose | 58% (4.9 vs.11.8)                                         | Significantly fewer cases of displaced abomasum (1.0% vs. 7.8%)           |
|                         |                                                 |                                                            |                                                                          |
| Agger et al., 1997      | Calcium chloride paste x 4 50 g Ca / dose        | 67% (14.3 vs. 42.9)                                         | Increased salivation following administration of the paste.              |
|                         |                                                 |                                                            |                                                                          |
| Agger, 1998             | Calcium chloride paste 1 x 3 + ½ x 2 50 or 25 g Ca / dose | 70% (10.0 vs. 33.3)                                         | Large number of cows (194 experimental cows and 713 control cows)         |
|                         |                                                 |                                                            |                                                                          |
| Pehrson et al., 1998    | Calcium propionate boli x 6 20 g Ca / dose       | 30% (25.3 vs. 36.0)                                         |                                                                          |
|                         |                                                 |                                                            |                                                                          |
|                         | Calcium chloride in oil x 4 54g Ca / dose       | 36% (23.2 vs. 36.0)                                         |                                                                          |
|                         |                                                 |                                                            |                                                                          |

¹) Preventive effect = 1 - RR = 1 – (incidence rate of milk fever among experimental cows / incidence rate of milk fever among control cows).
Calcium chloride gel product within 1 h of parturition. A significant (p<0.01) rise in serum total calcium was recorded within 5 min of administration. Serum calcium levels had returned to baseline values after 24 h. Thus a significant increase in serum Ca can be obtained very quickly. On the other hand, the biological effect is short-lived, which explains the risk of recurrence. Agger et al. (1997) discussed the short effect and believed it to be the result of an inhibition of the activation of those homeostatic mechanisms that should otherwise protect against parturient hypocalcaemia.

Chalk (calcium carbonate) does not provide readily absorbable calcium ions (Goff & Horst 1993). It most likely needs exposure to the acid in gastric juice to be dissociated and such calcium is therefore primarily available for absorption in the small intestine. The digestibility of such bound calcium is therefore dependent on the calcium absorption capacity of the small intestine. This capacity is controlled by the calcium homeostatic mechanisms, which, in case of the milk fever cow, are operating at an insufficient level. Simply increasing chalk supplementation to calving cows, or drenching them with such substances, is therefore unreliable in preventing milk fever. Accordingly recent studies (Thilsing-Hansen & Jørgensen 2001) have shown that milk fever was not prevented in control cows drenched with calcium carbonate after calving.

### Table 2. Controlled investigations on the prophylactic effect of oral calcium drenching supplementary to i.v. treatment on milk fever recurrence.

| Reference | Supplemental treatment | Preventive effect on milk fever recurrence<sup>1)</sup> | Comments |
|-----------|-----------------------|------------------------------------------------------|----------|
| Olsen and Jensen, 1965 | Calcium chloride solution (aq.) x 1, 126 g Ca / dose<sup>2)</sup> | 70% (7.6 vs. 25.0) | No apparent side-effects. Two different types of i.v. treatment were used. |
| Ringarp, 1965 | a) Calcium chloride solution (aq.) x 1, 54.5 – 109.0 g Ca / dose<sup>2)</sup> | 77% (12.8 vs. 55.6) | Different types of i.v. treatments in the two experiments (a and b). The amount of calcium given p.o. depended on the size of the cow. |
| b) Calcium chloride solution (aq.) x 1, 54.5 – 109.0 g Ca / dose<sup>2)</sup> | 65% (9.5 vs. 27.1) |
| Jonsgaard et al., 1971 | a) Calcium chloride gel x 1, 72.2 g Ca / dose<sup>2)</sup> | 45% (25.0 vs. 45.6) | Within each experiment (a and b) 4 different types of i.v. treatments were used. |
| b) Calcium chloride gel x 1, 111.9 g Ca / dose<sup>2)</sup> | 34% (29.9 vs. 45.6) |
| Chieze and Baudet, 1992 | Calcium chloride oil x 2, 50 g Ca / dose | 68% (7.7 vs. 24.3) |

<sup>1</sup> Preventive effect = 1 - RR = 1 – (incidence rate of milk fever recurrence among experimental cows / incidence rate of milk fever recurrence among control cows).

<sup>2</sup> The Ca dose was calculated based on information about the CaCl<sub>2</sub> dose.
oral calcium drenching against parturient hypocalcaemia.
The preventive effect is calculated as 1 minus the relative risk (RR), where RR is the incidence rate of milk fever among cows in the experimental group divided by the incidence rate of milk fever among cows in the control group. In the majority of these investigations the material used are either cows, which had milk fever at the previous calving, or cows of third or higher parity. A frequency of milk fever at 20%-50% may be expected among such cows (Hove 1986).

In the trials of Jönsson & Pehrson (1970), Simesen & Hyldgaard-Jensen (1971) and Oetzel (1996a) the programme of giving 3-10 doses of calcium chloride as a water-soluble gel has a preventive effect of approximately 50%-55%.

The early study of Ringarp et al. (1967) is given less weight because essential details for efficacy estimation were not well described. According to Pehrson et al. (1989) drenching with 4 doses of CaCl$_2$ / CaSO$_4$ in capsules seems to have slightly higher efficacy (73%).

Calcium chloride in a paste formulation was reported to have a preventive effect of about 70% in 2 investigations (Agger et al. 1997, Agger 1998), and calcium as a propionate paste was tested in 1 study with an efficacy of 42% (Goff et al. 1996). A propionate bolus product was similarly reported in a single study, with an efficacy of 30% (Pehrson et al. 1998). The preventive effect of 2 doses, a widely used practice, has apparently not been investigated.

The limitation of using the above mentioned compounds for oral Ca drenching is the toxicity, as discussed below.

Table 2 shows the preventive effect calculated from controlled investigations on oral calcium drenching supplementary to i.v. treatment of milk fever cases. These investigations are therefore concerned with the risk of clinical relapse in cows already treated by the veterinarian with intravenous calcium infusion. In an average cow population, the recurrence rate after 1st treatment is of the order of 30%-35% without supplementary oral treatment (Rajala & Gröhn 1998). In particular aged cows can be very hard to get on their feet, and the recurrence rate may be considerably higher, as in the study of Jonsgaard et al. (1971) (see Table 2).

In summing up the figures presented in Table 2, the mean preventive effect of such a post treatment drenching regime involving 1 or 2 oral doses against milk fever, recurrence may be assessed at approximately 60%.

Some dairy managers apply oral calcium drenching for a third purpose, i.e. for the tactical or preventive treatment of newly calved cows that appear to be borderline cases of milk fever. The early study of Glawischnig (1962) support the conviction of many herd managers that such use is effective, but controlled studies are lacking. Because of potentially decreased swallowing reflex and rumen motility in cows with borderline milk fever oral calcium drenching should be done with caution.

**Side effects.** Positive side effects following efficient milk fever prevention are reductions in hypocalcaemia-associated diseases and improved reproduction and production, as reviewed by Houe et al. (2001). Unwanted side effects following calcium chloride drenching were observed by Jørgensen et al. (1990) and later by Wentink & van den Ingh (1992). These side effects appeared when preparations containing calcium chloride in a concentrated form was used, and they were caused by a strong irritating effect on the mucous lining of the gastro-intestinal tract. Post mortem lesions vary in severity from focal haemorrhage to deep necrosis. Particularly severe lesions were seen after drenching with a commercial product based on calcium formate (Scott & Wijk 1999). Preparations containing
calcium chloride in oil emulsions appear to be less harmful than preparations containing calcium chloride in aqueous gel or plain aqueous solution (Jørgensen et al. 1990, Wentink & van den Ingh 1992), and the relatively low efficacy of propionate preparations should be weighed against the absence of reports on unwanted side effects after drenching with calcium propionate. The significance of most of the lesions in terms of cow welfare and production is frequently debated, but has not yet been investigated. The chloride ion from CaCl₂ is readily absorbed into the blood, and blood pH therefore decreases to maintain electroneutrality of the blood (Goff & Horst 1994). Besides the caustic effect on the mucous lining overdosing with calcium chloride preparations may therefore result in uncompensated systemic acidosis. Fatal cases due to application errors involving pharynx penetration, or lung aspiration of liquid products, are well known in practice but seldom reported in the literature (Hallgren 1965).

**Conclusion.** Oral drenching with calcium preparations can prevent a significant proportion of milk fever cases when given to parturient cows. Most documented preventive programmes involve administration of 3-4 doses distributed evenly during the period from 12-24 h before calving to 24 h after calving (Jönsson & Pehrson 1970, Pehrson et al. 1989, Goff et al. 1996, Oetzel 1996a, Agger et al. 1997). Oral calcium drenching can also prevent a significant proportion of relapses when given as a 1 or 2-dose supplement to intravenous calcium therapy of milk fever cases. General drawbacks of oral drenching are that single cow handling is necessary, and that there is a risk of aspiration pneumonia. As mentioned above, products based on calcium chloride (and calcium formate) may give rise to irritation of the gastrointestinal mucosa and uncompensated systemic acidosis.

### II. Acidifying rations (Dietary cation-anion difference, DCAD)

Under practical conditions this principle is applied by supplementing the dry cow ration with an anionic salt, or more common a mixture of salts, capable of acidifying the cow. The required amount of anionic salts is dependent on the DCAD of the prepartum ration, and it may, depending on the salt, range from around 50 to 500g (Houe et al. 2001). Although the time period of feeding the salts has ranged from 21 to 45 days in most studies, it may be possible to reduce the time period without losing the effect. It is suggested, however, that a feeding period of at least 10 days prepartum is required (Oetzel 1996b).

**Main mechanism and effect.** This principle, and the theories behind it, has been well described by others (Ender et al. 1971, Dishington 1975, Stewart 1983, Goff et al. 1991, Wang & Beede 1992a, Goff & Horst 1997, Horst et al. 1997). The cow must be brought into a physiological stage of compensated systemic acidosis. This is most efficiently achieved by the ingestion of rations having a surplus of acidifying anions. A useful method for determining whether an animal is responding to added dietary anions is to monitor urine pH. A urinary pH within the range 5.5 to 6.2 is accepted as an indicator of successful administration of anions (Horst et al. 1997).

Several methods for calculating the DCAD of the diet have been utilized, including the following equations:

\[
\text{DCAD (meq)} = (Na + K + Ca + Mg) - (Cl + SO_4 + H_2PO_4 + HPO_4) \\
\text{DCAD (meq)} = (Na + K + Ca + Mg) - (Cl + S + P) \\
\text{DCAD (meq)} = (Na + K + .38 Ca + .30 Mg) - (Cl + .60 S + .50 P) \\
\text{DCAD (meq)} = (Na + K) - (Cl + S) \\
\text{DCAD (meq)} = (Na + K) - (Cl)
\]
The equation most often used by dairy nutritionists is, however, the one considering 
(Na + K) – (Cl + S) (Oetzel 1996b).

During the years studies have been performed using a wide variety of anion sources (i.e. MgSO₄, MgCl₂, NH₄Cl, (NH₄)₂SO₄, CaCl₂, CaSO₄, HCl, H₂SO₄, AlSO₄). The mechanism by which the acidotic stage affects calcium metabolism and homeostasis is not fully understood, but it is suggested that the effect is mediated via an enhancement of the stimulatory effects of PTH (Horst et al. 1997). Increased plasma hydroxyproline concentration suggests that bone resorption may be involved (Leclerc & Block 1989), and some studies reported an increase in the apparent calcium absorption from the digestive tract (Verdaris & Evans 1976, Lomba et al. 1978), while others found no changes (Takagi & Block 1991), or even a decrease (Leclerc & Block 1989). The extensive urinary calcium excretion seen in cows fed anionic salts, may stimulate the vitamin D-related calcium homeostatic mechanisms, and in this way help prevent parturient paresis (Vagoni & Oetzel 1998)

Fig. 1 shows the incidence of milk fever obtained in experiments applying feed with different DCAD. Only studies in which the DCAD has been calculated by the formula (Na⁺ + K⁺) - (Cl⁻ + S⁻) is included. Looking at the distribution of the milk fever incidence in relation to the DCAD there is a clear tendency towards increasing milk fever incidence with increasing DCAD. As can be seen, keeping DCAD below zero results in a reduced milk fever incidence compared to a positive DCAD. The milk fever incidence varies significantly, ranging from 0 to 80 percent when the DCAD is positive, whereas...
the incidence appears to stay below 20 percent when the DCAD is negative. It appears from the figure, that the effect is unpredictable based solely on the absolute size in DCAD change, and that the effect apparently depends on whether the DCAD is kept below a certain limit. As a rule-of-thumb this limit is at zero. Calculating the relative risk (RR) of developing milk fever in each experiment including groups receiving feeds with DCAD below and above (or equal to) zero, results in a mean RR of approximately 0.35 in favour of the negative DCAD. In studies including more than 2 groups, the milk fever incidence rate among positive DCAD versus negative DCAD groups is used for calculating the RR. The study done by Leclerc & Block (1989) is not included in the calculations, as they did not include a group receiving feed with a negative DCAD. In 2 of the studies (Mosel et al. 1993 and Taurianen et al. 1998) the milk fever incidence was zero among cows in the positive as well as negative DCAD group (RR=1). Excluding these results from the calculations, the RR changes from 0.35 to 0.19. The true RR is probably to be found somewhere in between.

It should be noted, that Fig. 1 is based solely on the results obtained in 11 studies, and because of this it only represents a limited number of animals. Furthermore, the experimental conditions (diet, number of cows, parity, duration, previous cases of milk fever etc.) vary considerably between the different studies. For instance some studies included cows of second or first parity (Mosel et al. 1993, Taurianen et al. 1998, Moore et al. 2000), whereas others (Block 1984, Oetzel et al. 1988, Leclerc & Block 1989, Goff et al. 1991, Beede et al. 1992, Goff & Horst 1997, Goff & Horst 1998) only included "high risk" cows (≥ third parity). The interpretation of Fig. 1 should therefore be done with caution.

The optimum calcium level in combination with the feeding of acidifying rations

Regarding the optimal amount of dietary calcium in combination with a low DCAD, recommendations are conflicting. Most authors (En- der et al. 1971, Lomba et al. 1978, Block 1984, Oetzel et al. 1988, Beede 1992, Oetzel 1996b) recommend a high level of daily Ca intake. On the other hand Schonewille et al. (1994) and Rodriguez (1998) argue that low calcium and a low DCAD supplement each other and they therefore believe such a combination to be superior to the combination high Ca – low DCAD. Goff & Horst (1997) and Taurianen et al. (1998) question whether the dietary calcium level has any influence at all on the blood calcium concentration at parturition in cows on an acidifying ration. It is noted, however, that when limestone is used to achieve a high level of dietary calcium, the alkalinising effect of the added calcium carbonate may be a factor of consideration (Goff & Horst 1998a).

Side effects. The use of anions to reduce the DCAD is limited by problems with palatability of the anionic salts most commonly used (Oetzel & Barmore 1993). It may be added that the rather unnatural acidosis induced by the DCAD principle could possibly also contribute to a reduced feed intake.

Several studies have shown a negative effect on the dry matter intake (DMI) when adding anionic salts to the ration (Gaynor et al. 1989, Oetzel & Barmore 1993, Goff & Horst 1997, Taurianen et al. 1998, Moore et al. 2000), whereas others found no effect on DMI (Block 1984, Oetzel et al. 1988). VandeHaar et al. (1999) have shown that decreased feed intake and a negative energy balance before calving increase plasma NEFA and concentration of liver triglyceride at calving. This in turn may increase the risk also of displaced abomasum (Cameron et al. 1998), as well as mastitis, and retained placenta post partum (Dyk 1995).
**Conclusion:** In order for the cation-anion principle to work, a surplus of absorbable anions must be fed for at least 10 days prepartum to prevent the cow from being alkalinised. A DCAD of -100 meq/kg (calculated as (Na + K) – (Cl + S)) has been recommended (Horst et al. 1997). A general disadvantage of this principle is the low palatability of the anionic salts most commonly used. In general, reducing the DCAD by supplementation of anionic salts should only be attempted if the DCAD of the diet is below 250 meq/kg (Horst et al. 1997).

**III. Low calcium intake and low Ca/P in late pregnancy**

This principle is based on the theory of preventing the calcium homeostatic mechanisms from becoming quiescent during the dry period.

**Main mechanism and effect.** The calcium demand of the dry cow is very limited: 33 g/day per 500 kg body weight in the last 2 months of pregnancy (NRC, 1989). Most dry cow rations do, however, contain considerably larger amounts. When calcium intake extensively exceeds the requirements, the calcium demand can be met almost entirely by passive diffusion from the intestinal tract, rendering the calcium homeostatic mechanisms relatively inactive (Ramberg et al. 1984, Horst et al. 1994).

At calving the production of 10 litres of colostrum will result in a loss of 23 g of calcium in a single milking (Horst et al. 1997). This sudden and extensive draw on blood calcium must be replaced via increased intestinal calcium absorption and increased resorption of calcium from the bones. The reactivation of the calcium homeostatic mechanisms is, however, time-consuming. A significant increase in calcium absorption from the gut demands 24 h of preceding 1,25(OH)\(_2\)D stimulation, while a significant increase in bone resorption demands 48 h of PTH stimulation. In milk fever cows, these adaptation processes may take even longer (Reinhardt et al. 1988).

By feeding low calcium (<20 g/d) diets in the dry period, the calcium homeostatic mechanisms are activated before calving, and the cow is thus capable of absorbing calcium more efficiently from the intestinal tract as well as drawing calcium from the bone around the time of calving (Kichura et al. 1982). Oetzel (1991), however, claimed that diets extremely high as well as low in calcium decreased the incidence of milk fever. The apparent ability of high Ca diets to prevent milk fever has not been explained or documented.

The necessary period of exposure in order to obtain good preventive effect from feeding a low-Ca diet transpires from experiments using prepartum feeding periods of 14 days or more (Goings et al. 1974, Green et al. 1981, Kichura et al. 1982), whereas Green et al. (1981) suggested that a low-Ca feeding period of 7 days before calving was too short for prevention of parturient paresis.

Fig. 2 is based on the results of 13 studies concerned mainly with the effect of calcium intake in the dry period on the incidence of milk fever. Again the interpretation of the figure must be done with caution, as the experimental conditions of the implicated studies are very diverse. There is, however, a clear tendency towards a very low milk fever incidence following a daily calcium intake below 20 g/d. In contrast, manipulation with the calcium intake above this level will not ensure a low incidence of milk fever. Among the reviewed studies the mean milk fever incidence in cows fed dry cow rations low in calcium (<20g/d) is 1.7 per cent, whereas the mean incidence among cows fed rations with a calcium content above 20g/d is 32.4 per cent (ranging from 0 to 80 per cent). These percentages should not be regarded as the absolute truth, as the experimental condi-
The significant difference in milk fever incidence is, however, a clear indication of the effect of keeping the dietary Ca below 20 g/d. Calculating the relative risk (RR) of developing milk fever in each experiment including groups with a daily calcium intake below as well as above 20 g/d results in a mean RR of 0.20 in favour of the low Ca intake. In studies including more than 2 groups, the mean milk fever incidence rate among low Ca (<20g/d) versus high Ca (>20g/d) groups was used for calculating the RR. Only 6 of the 13 studies operated with groups below as well as above 20 g/d. In 4 of these studies the RR was 0. One study (Green et al. 1981) was omitted because of uncertainty of the interpretation of the results, and in the last study the RR was 1 due to a lack of milk fever in both groups. This study therefore has a large effect on the mean RR, and excluding this study from the calculations would result in a RR of 0.

The true relative risk is probably to be found somewhere between 0 and 0.20. Because of problems in keeping the calcium intake sufficiently low using commercial available feeds, the low-Ca principle has been more or less abandoned in many countries. However, recent studies attempt to revive the low calcium principle by introducing induced reduced ration calcium availability by the addition of a calcium binder to the ration (Jørgensen & Thilsing-Hansen 2000, Thilsing-Hansen & Jørgensen 2000, Jørgensen et al. 2001, Thilsing-Hansen & Jørgensen 2001, Wilson 2001).

The Ca/P ratio has been suggested as another important factor in the development of milk fever. Early studies (Boda & Cole 1954, Stott 1965) stressed the importance of keeping the dietary Ca:P ratio low in preventing parturient paresis. It was suggested that a high dietary P suppressed vitamin D hydroxylation in the kidney, thereby indirectly reducing calcium ab-

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Figure 2. The influence of dietary calcium in the dry period on the incidence of milk fever. Results from 13 studies.
sorption. The reduced intestinal Ca absorption elicited an increase in PTH level, which in turn aided in the prevention of milk fever (Gerloff 1988). Kichura et al. (1982) on the other hand, stated that the beneficial effect of feeding low Ca diets appeared independent of P. In addition they found that low dietary phosphorus seemed helpful in preventing parturient paresis, when dietary calcium was high. It was suggested that the low dietary phosphorus resulted in an increased formation of 1,25(OH)\textsubscript{2}D, which in turn increased the efficiency of intestinal absorption of calcium and phosphorus. This viewpoint was supported by Barton et al. (1987) who found that although low dietary phosphorus did not prevent milk fever, the postpartum calcium and phosphorus homeostasis was enhanced, and by Curtis et al. (1984) in their epidemiological study of factors predisposing to parturient paresis.

As shown above there are many different opinions about the influence of the Ca/P ratio on the incidence of milk fever. In conclusion, the absolute amount of calcium in the diet is probably more important than the Ca/P ratio (Allen & Davies 1981).

**Conclusion:** The low calcium principle is highly effective, approaching 100%, in preventing milk fever provided the daily calcium intake is kept below 20 g/d, and provided the exposure period includes at least the last 2 weeks before calving. Using commonly available feeds a calcium level of <20g/d is difficult to obtain. A possible solution to this problem may be the addition of a calcium binder to the feed. Regarding the influence of the Ca/P ratio, it is concluded that the absolute amount of calcium in the diet is apparently more important.

**IV. Prepartum administration of vitamin D, vitamin D metabolites and analogues**

The use of large doses of vitamin D metabolites and analogues for milk fever prevention is controversial. Efficacies vary greatly between studies and the dose required is very close to the toxic dose causing clinical symptoms (Little-dike & Horst 1982) including marked anorexia, loss of body weight, dyspnoea, tachycardia, recumbency, torticollis and severe cardiovascular calcifications (Greig 1963, Seekles & Wilson 1964, Payne & Manston 1967, Radostits et al. 2000). The timing of the treatments is very important. Injection given 2-8 days before parturition has been considered optimal. If the cow fails to calve after the 8\textsuperscript{th} day, another injection may be given and repeated every 8 days until calving (Radostits et al. 2000). For security reasons most producers of these products do, however, not recommend the use of more than 2 doses per cow. Another potential problem in utilizing the vitamin D family of compounds is the risk of hypocalcaemia and clinical signs of milk fever 10-14 days post partum (Hove & Kristiansen 1984, Goff et al. 1988). Among these hypocalcaemic animals the plasma 1,25(OH)\textsubscript{2}D\textsubscript{3} is not increased. The animal is apparently dependent on exogenous 1,25(OH)\textsubscript{2}D\textsubscript{3} to reverse its hypocalcaemia (Goff et al. 1988). Despite these drawbacks, vitamin D3 injection has been the most commonly used method of prevention, principally because of its simplicity (Radostits et al. 2000).

Because of the unwanted side effects, and because of an almost total lack of more recent controlled studies dealing with such side effects, production implications and consumer safety, the principle is not described further in this review. Readers are referred to the description given by Radostits et al. (2000).

**V. Peripartum dietary magnesium control**

Some herds with chronic hypomagnesaemia problems have been known to have very high incidences of milk fever, sometimes approaching 80%-90% of all calvings (Allen & Davies 2000).
Subclinically hypomagnesaemic cows are less able to mobilise calcium in response to hypocalcaemia (Contreras et al. 1982, Sansom et al. 1982, Braak et al. 1987b), and chronic hypomagnesaemia can have deleterious effects on calcium homeostasis (Reinhardt et al. 1988). More specifically, Braak et al. (1987a) found that the resorptive activity of the bones of magnesium deficient cows was significantly depressed, and Mosel (1991) found that a slight degree of hypocalcaemia coupled with a greater degree of hypomagnesaemia could lead to clinical signs similar to those of severe periparturient hypocalcaemia.

**Conclusion:** Although magnesium is not directly involved in the aetiology of milk fever, checking of magnesium status should be part of a milk fever control programme since all studies indicate the importance of supplying the periparturient cow with sufficient magnesium to fulfil its needs. The recommended magnesium content of the diet for pregnant dry cows is 0.16% of DM intake (NRC, 1989). Wang & Beede (1992b) found no improving effect on the calcium metabolism from feeding a high Mg diet (0.37% of DM) compared to a normal Mg diet (0.2% of DM) when the cows were fed acidogenic diets. With regard to Mg administration it is further important not to feed roughage from pastures over-fertilised with potassium, as a high [K+] decreases the uptake of magnesium (Allan & Davies 1981).

**VI. Body condition control**

Over-conditioned cows at calving have a higher incidence of milk fever (Harris 1981) and other diseases postpartum (Thatcher 1986, Studer 1998, Rukkwamsuk et al. 1999). Heuer et al. (1999) found that over-conditioned cows (body condition score (BCS) ≥4) had a 3.3 times higher risk of contracting milk fever. Accordingly, Østergaard & Gröhn (1999) found a relatively higher body weight in cows contracting milk fever. The most likely explanation for the increased risk of milk fever in over-conditioned cows is a low calcium intake caused by reduced appetite in the critical period around calving (Rukkwamsuk et al. 1999).

**Conclusion:** It is important to prevent the dry cows from being too fat. It is therefore recommended that the energy intake of cows in mid and late lactation is controlled to ensure a BCS of ≤3.75. Optimum BCS has been proposed to be 3.25 to 3.75 (Studer 1998). However, if over-conditioned, cows in the late dry period should maintain body condition to prevent fatty liver (Studer 1998).

**VII. Controlling dietary carbohydrate intake peripartum**

The influence of concentrate or grain feeding in the dry period was reviewed by Houe et al. (2001). Results of studies concerned with the influence of carbohydrate feeding on the incidence of milk fever are conflicting. Kendall et al. (1966) found that grain fed at 1% of body weight reduced the incidence of milk fever, and Barnouin & Chassagne (1991) found an increased risk of milk fever in cows fed rations high in green fodder and calcium but low in cereals. On the other hand Jönsson & Pehrson (1983) found that a 100% overfeeding with energy (and 80% overfeeding with protein) during the last 8 weeks of pregnancy resulted in an increased incidence of parturient paresis. Accordingly Braak et al. (1986a, 1986b) found that overfeeding cows prepartum increased the incidence of milk fever. Curtis et al. (1985) found no effect of energy intake prepartum.

**Conclusion:** The informations are conflicting. Most authors do, however, believe that feeding large amounts of concentrate in the dry period leads to higher incidences of milk fever. The reason might be that "overfed" cows more eas-
ily loose appetite around calving and thereby absorb less calcium than required (Allen & Davies 1981, Braak et al. 1986b). Limiting energy intake prepartum will according to Coppack et al. (1972) prevent not only parturient paresis but also displaced abomasum.

VIII. Shortening of the dry period
The influence of the length of the dry period on milk fever was reviewed by Houe et al. (2001). Cows with long non-lactating periods are predisposed to becoming excessively fat, since cows do not regulate intake according to their physiological requirements (Morrow et al. 1979). Besides obesity, a long dry period may result in a more quiescent calcium homeostasis. Davicco et al. (1992) found a less profound post parturient drop in blood calcium of cows with a mean dry period of 4 days only as compared to a period of 8 weeks. There are, however, some side effects from reducing the length of the dry period. Sørensen & Enevoldsen (1991) reported a significant reduction in milk production in the subsequent lactation when shortening the dry period from 7 to 4 weeks.

IX. Prepartum milking
Prepartum milking has been found to have no effect on the incidence of milk fever (Smith & Blosser 1947, Eaton et al. 1949, Ackerman et al. 1955), whereas others found a decrease in milk fever incidence following prepartum milking (Smith & Keyes 1953, Greene et al. 1988). Most studies on prepartum milking showed no effect on lactation milk yield (Smith & Keyes 1953, Zeliger et al. 1973, Greene et al. 1988), whereas the effect on retained placenta and under oedema varies among studies. However, most of these studies are fairly old. In the large study by Greene and co-workers (1988) it was concluded that prepartum milking can be practiced with no detrimental effects, but as there is no positive effect on lactation milk yield, prepartum milking is unlikely to be justified economically.

Conclusion: Shortening of the dry period as well as prepartum milking is unlikely to serve as an option in future herd control programmes, including programmes for milk fever prevention, unless the effect is documented by thorough cost-benefit calculations.

X. Reduced milking in early lactation
Although easy to apply, an effect of reduced milking in early lactation is questionable. Hemslay (1957) and Jonsgaard (1972) found no effect of the degree of milking after i.v. calcium treatment on the incidence of milk fever relapses. As no recent studies have been performed on this subject it is not evaluated further in this review.

General conclusions
The 3 most frequently used principles in Denmark for preventing milk fever are: Oral calcium drenching around calving, feeding acidifying rations (Dietary cation–anion difference, DCAD) and feeding rations low in calcium. Oral calcium drenching around calving should preferably be done as recommended in the reference studies i.e. 3-4 times for milk fever prevention and 1-2 times for prevention of milk fever relapse. Giving fewer drenches may have some preventive effect, but it is unlikely to reach the effect of the full programme.

When using the cation-anion principle it is of crucial importance to feed a surplus of absorbable anions to convert the cow from being alkaline to moderately acidotic. The palatability of the anionic salts most commonly used limit the use of this principle. In general it should not be implemented on rations with a DCAD above 250 meq/kg DM.

When using the low-Ca principle, daily calcium
intake should be below the requirements of the dry cow. Although difficult to obtain when using commonly available feeds, a daily intake of 20 g/d (or below) is recommended. Unfortunately the above mentioned recommendations are rarely met in practice, resulting in low efficacy measures. Besides palatability problems and difficulty in formulating low-Ca rations, reasons for not following the recommendations may be found in economic considerations and time-consuming single cow handling. These issues have to be thoroughly considered when choosing the method for milk fever prevention on each farm. The preventive principle suitable on one farm is not necessarily suitable on another. Even when applied in the most optimal way the preventive effect of the described principles rarely reaches 100 per cent. Combining one or more of the principles is one potential way of improving efficacy. The low-Ca principle combined with oral calcium drenching around calving could be one option, whereas drenching cows on a negative DCAD ration with oral CaCl₂ is discouraged by Pehrson et al. (1999) due to the risk of inducing an uncompensated metabolic acidosis. Finally, recommendations are conflicting regarding the combined feeding of an acidified ration containing a minimum of calcium. Although not uniquely designed for milk fever prevention certain management measures may be combined with the above-mentioned primary preventive principles. There is only limited information about how the different principles are most efficiently implemented as detailed strategies. It is very much up to the individual farmer or adviser to choose which principle to use. Hopefully, the future will bring more detailed information on the optimal use of control strategies under different farming conditions.

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Sammendrag

Principper for kontrol af mælkefeber. En litteratur-oversigt.

I dette review blev 3 hyppigt anvendte forebyggende principper mod mælkefeber gennemgået: Oral calcium tildeling i tiden omkring kælvning, tildeling af forsurende rationer (DCAD = dietary cation-anion difference) samt tildeling af rationer med lavt calciumindhold i goldperioden. Effektiviteten af hvert princip blev estimeret ud fra resultaterne af kontrollerede forsøg.

Oral calcium tildeling i tiden omkring kælvning har tilsyneladende en effektivitetsomkring 50%-60%, hvad angår forebyggelse af mælkefeber såvel som forrebyggelse af tilbagefald efter i.v. behandling med calciumpræparater. Forsøg har vist, at visse af præparaterne har bivirkninger i form af lésioner i forma- verne. Betydningen af disse lésioner er endnu ikke undersøgt.

Ved anvendelse af forsurende rationer i goldperioden vil rationer med DCAD (beregnet som (Na + K) – (S + Cl)) under 0 sænke mælkefeberincidenccen signifikan. Udfra de kontrollerede forsøg inkluderet i dette review er den relative risiko (RR) for at udvikle mælkefeber blandt koer fodret med rationer med DCAD<0 i forhold til koer fodret med rationer med DCAD>0 estimeret til at ligge mellem 0.19 og 0.35. Dog varierer mælkefeberincidenccen voldsomt (0%-80%) blandt koer fodret med rationer med positiv DCAD. Det primære problem forbundet med anvendelsen af DCAD principippet er smagelighedsproblemerne.

Tildeling af goldrationer med lavt calciumindhold er meget effektivt til forebyggelse af mælkefeber, forudsat det daglige calciumindtag ikke overstiger 20g/d i goldperioden. Blandt de i reviewet inkluderede undersøgelser var den relative risiko for udvikling af mælkefeber blandt koer med dagligt Ca-indtag under 20g/d i forhold til koer med dagligt Ca-indtag over 20g/d estimeret til at ligge mellem 0 og 0.2. Dog var mælkefeberincidenccen stærkt variérer blandt koer med dagligt Ca-indtag over 20g/d (0%-80%). Problemet forbundet med implementering af Lav-Ca principippet er, at de hyppigst anvendte fodermidler til kvæg har et højt indhold af calcium, hvilket gør det vanskeligt at formulerere rationer til utilstrækkelig lavt calciumindhold.

Anvendelse af vitamin D samt vitamin D metaboliter og analoger til forebyggelse af mælkefeber er på grund af toxicitetsproblemer samt mangler på nyere undersøgelser kun behandlet kort i dette review. Ud over de ovennævnte forebyggelsesprincipper blev enkelte managementrelaterede emner med relation til mælkefeberforebyggelse diskuteret, og følgende konklusioner blev dragent: Det er vigtigt at tildele den drægtige goldko tilstrækkeligt med magnesium samt at undgå, at goldkoerne bliver for fede. Tilgængelige informationer vedrørende betydningen af kulhydratindtaget, længden af goldperioden og malkning inden kælvning for udviklingen af mælkefeber er for utilstrækkelige til, at disse faktorer på nuværende tidspunkt kan inkluderes i mælkefeberkontrolprogrammer.

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