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A meta-analysis of the effects of Vitamin E supplementation on the incidence of retained foetal membranes in dairy cows

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Abstract

A meta-analysis was performed to consolidate the results of studies which have evaluated the effects of Vitamin E supplementation during the dry period on the risk of retained foetal membranes (RFM) in the dairy cow. Twenty studies demonstrated a beneficial response to Vitamin E whilst 21 found no benefit and 3 reported an increase in the incidence of RFM in treated cows. The odds ratios (OR) of the available studies exhibited significant heterogeneity, so multivariable logistic regression analysis was performed to enable the identification of factors associated with the response to Vitamin E supplementation. Our multivariable analysis included parity and Vitamin E supplementation (control/treated) in the model, because all other factors were co-linear. Results indicated that Vitamin E supplementation led to a reduction in the incidence of RFM. A second multivariable analysis was undertaken on a subset of the data including only supplemented cows to determine the influence of supplementation factors on the risk of RFM. All factors were co-linear with each other, therefore, only type of Vitamin E supplementation was included in this analysis. The regression model demonstrated that administration of the synthetic Vitamin E α-tocopheryl acetate was associated with a lower risk of RFM than treatment with natural Vitamin E (α-tocopherol) ($P = 0.047$, OR = 0.49), whereas the difference between the synthetic Vitamin E α-tocopherol acetate and natural Vitamin E just failed to attain statistical significance ($P = 0.059$, OR = 0.53). Overall the analyses indicate that Vitamin E supplementation during the dry period is associated with a reduced risk of RFM, and that the synthetic forms of Vitamin E are more effective than the natural compound.

Keywords: Vitamin E; Meta-analysis; Retained foetal membranes; Dairy cow; Multivariable logistic regression analysis

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1. Introduction

Retained foetal membranes (RFM) is usually defined as the inability of the cow to expel the foetal membranes within 24 h following parturition [1]. Approximately 80% of all cases of RFM occur due to failure of the maternal-foetal union to separate, whilst 20% occur due to either entrapment of the membranes at the cervix or reduced strength of myometrial contractions [1]. Subsequent reproductive performance is reduced in cows which retain their foetal membranes. Such cows are more likely to develop metritis or endometritis, have a longer post-partum interval to ovulation and have an increased calving-to-conception interval [2]. The average incidence of RFM in the UK is estimated to be between 4 and 8% [1]. The high cost of each case of RFM emphasises the need for prophylactic treatments to reduce the risk of disease [3].

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An increase in the incidence of RFM has been linked to areas with a high incidence of nutritional muscular dystrophy. This disease is associated with a deficiency in selenium or Vitamin E; thus, an increased incidence of RFM was thought to be associated with a deficiency of Vitamin E or selenium in the cow [4]. Vitamin E and selenium work synergistically and have similar yet independent roles in protecting tissues from oxidative damage [5].

A decrease in blood concentrations of Vitamin E has been reported in the last 2 weeks before calving [6]. At the same time, there is a reduction in the ability of the immune system to respond to infection associated with a reduction in superoxide production and killing ability of neutrophils [7]. In-feed or injectable supplementation of Vitamin E in the last 4–6 weeks of gestation can prevent the decline in blood Vitamin E concentrations and enhance the killing ability of neutrophils [8].

Many studies have investigated the effect of Vitamin E supplementation on the incidence of RFM; however, the results published have not been consistent. These inconsistencies might be related to many factors including nutrition, management, breed or age of cattle or the cause of RFM. If Vitamin E is found to be of benefit in reducing the risk of RFM, it might be used as a relatively low cost prophylactic treatment and thus increase dairy cow fertility and profitability and, more importantly, improve dairy cow welfare. We carried out a meta-analysis to consolidate results of previous studies assessing the effects of Vitamin E supplementation on the incidence of RFM in dairy cows. Such an analysis should identify the factors causing the inconsistencies between previous studies and thus help to identify target groups of dairy cattle that might benefit from Vitamin E supplementation.

2. Materials and methods

Papers of all languages, providing an abstract in English, published after 1972 were sought using the online journal databases Web of Science (ISI, UK), Medline (US National Library of Medicines) and CAB (CABI Publishing). Further papers were found by cross-referencing citations in retrieved articles. All non-English papers were translated. To obtain unpublished studies, and thus reduce publication bias, an attempt was made to contact all authors of papers found. No unpublished studies could be located. Twenty-two journal articles describing 44 studies that met the following criteria were included in the meta-analysis. To be included all papers had to meet the following criteria: (a) treated cows received Vitamin E supplementation during the dry period or immediately after calving; (b) data on a group of control cows were included; (c) cows were allocated at random to the supplemented group; (d) the number of cows in both control and treated groups retaining their foetal membranes was recorded. Although the length of time to define a RFM case varied, the minimum and maximum periods were 6 and 24 h, respectively. All study reports indicated Vitamin E supplementation was given in the dry period but the route, amount, type and timing varied between studies. To maximise the number of studies included in the analysis, an initial multivariable analysis (Analysis 1) was conducted in which treatment was defined as any type of Vitamin E administered at any time during the dry period. The studies selected for this analysis utilised a range of different Vitamin E treatment protocols. The amount of Vitamin E and selenium supplemented was categorised by ranking the studies and dividing doses into approximate tertiles. Vitamin E supplementation was categorised into <680 IU, 680 IU and >680 IU, the smallest dose was 70 IU and the maximum dose was 3000 IU. Selenium supplementation doses were divided into none, <25 and >25 mg, the maximum dose being 50 mg. Due to the complexity of dietary details, studies were divided into those using intensive feeding, where concentrates were fed, and non-intensive, where silage, pasture or hay only was supplied. Details of management and supplementation protocols are summarised in Table 1.

An odds ratio, assessing the effect of Vitamin E supplementation on the incidence of RFM, was calculated for each study. The assumption that individual odds ratios were homogenous across study populations was statistically tested by deriving the heterogeneity statistic (G), which exhibits a χ^2 distribution [9]. A quadrature check was then used to determine whether a random effects logistic regression analysis could be used to determine the sources of heterogeneity. A generalised estimating equation (GEE) approach with robust standard errors was used for analysis.

Univariable analyses were conducted on the five categorical variables (Table 2) and those significant at $P < 0.25$ were assessed for co-linearity with each other using the chi-squared test. For pairs of variables found to be significantly associated with each other ($P \leq 0.05$), the variable deemed the most biologically plausible was used as a candidate in the GEE analysis. These variables were tested for significance in the model using a Wald test [10].

Table 1
Details of management and supplementation protocols for each study

Study	Vitamin E amount[a] (IU)	Vitamin E type	Route	Timing[b]	Selenium amount[a] (mg)	Size of study	Age of cows	Breed	Feed
1	680	α-Tocopherol acetate	Intra-muscular	28	<25	65		Friesian	Non-intensive
2	680	α-Tocopherol acetate	Intra-muscular	28	<25	35		Frisian	Non-intensive
3	680	α-Tocopherol acetate	Intra-muscular	30	>25	92		Other	
4	680	α-Tocopherol acetate	Intra-muscular	30	>25	60		Other	
5	680	α-Tocopherol acetate	Intra-muscular	30	>25	23		Other	
6	<680	α-Tocopheryl acetate	Intra-muscular	20	<25	72	Primiparous	Holstein	
7	<680	α-Tocopheryl acetate	Intra-muscular	20	<25	168	Multiparous	Holstein	
8	<680	α-Tocopheryl acetate	Intra-muscular	20	<25	35	Primiparous	Holstein	
9	<680	α-Tocopheryl acetate	Intra-muscular	20	<25	104	Multiparous	Holstein	
10	>680	α-Tocopheryl acetate	Intra-muscular	20	<25	54	Primiparous	Holstein	
11	>680	α-Tocopheryl acetate	Intra-muscular	20	<25	166	Multiparous	Holstein	
12	<680	α-Tocopherol acetate	Intra-muscular	20	<25	58	Primiparous	Holstein	Intensive
13	<680	α-Tocopherol acetate	Intra-muscular	20	<25	60	Primiparous	Holstein	
14	<680	α-Tocopherol acetate	Intra-muscular	20	<25	57	Primiparous	Holstein	
15	<680	α-Tocopherol acetate	Intra-muscular	20	<25	124	Multiparous	Holstein	
16	<680	α-Tocopherol acetate	Intra-muscular	20	<25	126	Multiparous	Holstein	
17	<680	α-Tocopherol acetate	Intra-muscular	20	<25	123	Multiparous	Holstein	
18	>680	α-Tocopherol	Intra-muscular	11	None	137	Primiparous	Holstein	
19	>680	α-Tocopherol	Intra-muscular	11	None	283	Multiparous	Holstein	
20	680	α-Tocopherol acetate	Intra-muscular	28	<25	140	Multiparous	Friesian	Intensive
21	680	α-Tocopheryl acetate	Intra-muscular	21	>25	198	Multiparous	Holstein	Intensive
22	680	α-Tocopherol acetate	Intra-muscular	20	>25	77	Multiparous	Holstein	
23	680	α-Tocopherol acetate	Intra-muscular	20	>25	217	Multiparous	Holstein	
24	680	α-Tocopherol acetate	Intra-muscular	20	>25	146	Multiparous	Holstein	
25	680	α-Tocopherol acetate	Intra-muscular	20	>25	31	Multiparous		Intensive
26	680	α-Tocopherol acetate	Intra-muscular	25	>25	57		Holstein	Non-intensive
27	>680	α-Tocopheryl acetate	Subcutaneous	7	None	1142			
28	<680		Intra-muscular	0	<25	40	Multiparous	Crossbreed	
29	>680	α-Tocopheryl acetate	In feed	60	None	40	Multiparous	Other	Intensive
30	680	α-Tocopheryl acetate	Intra-muscular	21	>25	82		Holstein	
31	680	α-Tocopherol acetate	Intra-muscular	21	>25	195			Intensive
32	>680	α-Tocopheryl acetate	In feed	60	None	39	Multiparous		Intensive
33	<680	α-Tocopheryl acetate	Intra-muscular	17	>25	50			
34	>680	α-Tocopherol	Intra-muscular	16	>25	407		Crossbreed	Non-intensive
35	>680	α-Tocopheryl acetate	In feed	42	None	36		Other	Intensive
36	<680	α-Tocopheryl acetate	In feed	60	None	76		Holstein	Intensive
37	>680		Intra-muscular	21	>25	60		Holstein	
38	<680		Intra-muscular	20	None	60		Holstein	
39	<680		Intra-muscular	20	>25	60		Holstein	
40	680	α-Tocopherol	Intra-muscular	28	>25	106		Holstein	
41	680	α-Tocopherol	Intra-muscular	28	>25	139		Holstein	
42	680	α-Tocopherol	Intra-muscular	28	>25	119		Holstein	
43	680	α-Tocopherol	Intra-muscular	28	>25	464		Holstein	
44	>680	α-Tocopherol	Intra-muscular	28	None	413		Holstein	

[a] One off dose with the exception of studies 29, 32, 35 and 36.

[b] Days prior to expected calving date.

A subset of the data, including only treated animals, underwent similar univariable, co-linearity and multivariable analyses (Analysis 2) to determine the influence of supplementation protocol, for example the type of Vitamin E supplemented, on the risk of RFM among treated animals.

Descriptive statistical analysis was completed using SPSS Version 11 (SPSS Inc., Chicago, USA), whilst the

Table 2
Variables from the studies included in this meta-analysis that underwent individual screening in a univariable analysis

Study variables		Significance in univariable regression	
		All animals (Analysis 1)	Treated animals only (Analysis 2)
Vitamin E supplementation	Control; Vitamin E supplementation	$P < 0.001$	–
Parity	Primiparous; multiparous	$P = 0.004$	$P = 0.013$
Breed	Holstein; Friesian; crossbred; other	$P = 0.148$	$P = 0.016$
Housing	Individually; grouped	$P = 0.052$	$P < 0.001$
Feed	Non-intensive; intensive	$P = 0.054$	$P = 0.011$
Route of Vitamin E administration	Intramuscular; subcutaneous; in feed		$P = 0.093$
Amount of Vitamin E supplemented	<680 IU; 680 IU; >680 IU		$P = 0.418$
Time	Continuous		$P < 0.001$
Type of Vitamin E supplemented	α-Tocopherol (natural); α-tocopherol acetate (synthetic); α-tocopheryl acetate (synthetic)		$P < 0.001$
Selenium supplementation	None; ≤25 mg; >25 mg		$P < 0.001$

multivariable analysis was completed using the STATA statistical package, Version 8 (StataCorp LP, Texas, USA).

3. Results

The odds ratios for each study are shown in Table 3. Whilst 20 studies indicated a positive association between supplementation and the risk of RFM, 3 studies reported a negative association and 21 found no significant association at $P < 0.10$.

The heterogeneity statistic for these 44 studies (G) was 133 ($P < 0.001$) indicating that the odds ratios differed significantly from each other. A quadrature check found that a random effects logistic regression analysis was unstable for this dataset (relative difference >0.01).

For Analysis 1, a univariable analysis determined that all factors tested (supplementation, parity, breed, housing and feed) showed some association with the risk of RFM at $P < 0.25$ (Table 2). These factors were assessed for co-linearity, which showed that all pairs of factors were collinear with each other ($P < 0.01$) with the exception of supplementation. Parity (first calving or multiparous) was selected as the most biologically relevant factor to include, alongside supplementation, in the multivariable model. This final GEE model contained 2495 observations on supplementation and parity. Supplemented cattle had a significantly reduced of RFM (OR = 0.47, CI 0.33–0.67, $P < 0.0001$). Although multiparous cows tended to have a higher risk of RFM than cows calving for the first time, regardless of supplementation, this difference was not significant (OR = 1.47, CI 1.16–2.11, $P = 0.154$) (Table 4).

The univariable analysis for Analysis 2 investigated only treated animals. Additional variables included which related to the type of Vitamin E treatment given were route of administration, amount, time in relation to calving, type of Vitamin E and the additional inclusion of selenium. The initial analysis concluded that all but two factors were significantly associated with the risk of RFM (Table 2). Co-linearity, however, existed between all factors, thus only type of Vitamin E was included in a final multivariable analysis, as this was deemed most biologically relevant. This model contained 2558 observations. Results indicated that treatment with either type of synthetic Vitamin E (α-tocopherol acetate and α-tocopheryl acetate) was associated with a lower risk of RFM compared with treatment with natural Vitamin E (α-tocopherol) (OR = 0.53 and 0.49, CI 2.75–0.02 and 0.24–0.99, $P = 0.059$ and 0.047, respectively) (Table 5).

4. Discussion

Much work has been undertaken on the effect of Vitamin E supplementation (with or without selenium) on the incidence of RFM. The literature search for this analysis alone identified 44 studies which complied with the specific criteria outlined above. However, there was a significant variation in findings between studies which limits the conclusions that can be drawn from a simple analysis. Thus, the data are ideal for a meta-analysis. Meta-analyses are of great value as the large combined sample size is greater than those of individual studies resulting in an increased power of investigation and an improved chance of extracting significant effects [11]. This is of particular importance when assessing a disease of low prevalence, as in the case of RFM, which

Table 3
The incidence and odds ratios of RFM for each study included in this meta-analysis

Study (Ref.)	Number of animals in study	Incidence of RFM		OR	OR		Chi square	Effect[a]
		Control	Supplemented		Confidence	Interval		
1 [11]	65	19 of 45	0 of 20	0.000	−0.736	0.736	<0.001	+
2 [11]	35	7 of 19	1 of 16	0.114	−2.114	2.343	0.037	+
3 [12]	92	16 of 39	6 of 53	0.184	−0.879	1.246	0.001	+
4 [12]	60	12 of 23	4 of 37	0.111	−1.210	1.433	0.001	+
5 [12]	23	7 of 9	0 of 14	0.000	−1.657	1.657	<0.001	+
6 [13]	72	2 of 36	1 of 36	0.486	−1.961	2.932	0.500	0
7 [13]	168	25 of 92	7 of 76	0.272	−0.631	1.175	0.002	+
8 [13]	35	1 of 17	1 of 18	0.941	−1.914	3.796	0.743	0
9 [13]	104	24 of 55	7 of 49	0.215	−0.746	1.177	0.001	+
10 [13]	54	7 of 32	1 of 22	0.170	−2.004	2.344	0.081	+
11 [13]	166	13 of 90	11 of 76	1.002	0.134	1.871	0.584	0
12 [13]	58	9 of 29	2 of 29	0.165	−1.473	1.802	0.021	+
13 [13]	60	9 of 29	4 of 31	0.329	−0.983	1.641	0.082	+
14 [13]	57	9 of 29	3 of 28	0.267	−1.166	1.700	0.059	+
15 [13]	124	17 of 63	6 of 61	0.295	−0.715	1.305	0.012	+
16 [13]	126	17 of 63	10 of 63	0.511	−0.365	1.386	0.096	+
17 [13]	123	17 of 63	16 of 60	0.984	0.186	1.782	0.565	0
18 [14]	137	9 of 75	1 of 62	0.120	−1.975	2.215	0.019	+
19 [14]	283	18 of 141	12 of 142	0.631	−0.140	1.402	0.162	0
20 [15]	140	35 of 79	4 of 61	0.088	−1.019	1.195	<0.001	+
21 [15]	198	10 of 99	3 of 99	0.278	−1.044	1.600	0.041	+
22 [16]	77	7 of 34	7 of 43	0.750	−0.410	1.910	0.422	0
23 [16]	217	28 of 110	16 of 107	0.515	−0.168	1.198	0.039	+
24 [16]	146	5 of 72	16 of 74	3.697	2.633	4.761	0.010	−
25 [17]	31	10 of 26	0 of 5	0.000	−1.180	1.180	0.120	0
26 [18]	57	8 of 29	9 of 28	1.243	0.107	2.380	0.465	0
27 [19]	1142	82 of 571	86 of 571	1.057	0.730	1.385	0.401	0
28 [20]	42	5 of 20	3 of 20	0.529	−1.061	2.120	0.347	0
29 [21]	40	7 of 20	2 of 20	0.206	−1.519	1.932	0.064	+
30 [22]	82	13 of 42	9 of 40	0.648	−0.342	1.637	0.270	0
31 [23]	195	19 of 96	22 of 99	1.158	0.468	1.848	0.405	0
32 [24]	39	3 of 19	4 of 20	1.333	−0.316	2.983	0.531	0
33 [25]	50	5 of 25	4 of 25	0.762	−0.689	2.212	0.500	0
34 [26]	407	46 of 217	47 of 190	1.222	0.759	1.685	0.233	0
35 [27]	36	3 of 18	3 of 18	1.000	−0.753	2.753	0.671	0
36 [28]	76	11 of 38	14 of 38	1.432	0.470	2.394	0.313	0
37 [29]	60	10 of 29	3 of 31	0.204	−1.212	1.619	0.021	+
38 [30]	60	9 of 30	8 of 30	0.848	−0.276	1.973	0.500	0
39 [30]	60	9 of 30	4 of 30	0.359	−0.952	1.670	0.105	0
40 [31]	68	29 of 36	9 of 32	0.094	−1.035	1.224	<0.001	+
41 [31]	119	17 of 92	3 of 27	0.551	−0.759	1.862	0.280	0
42 [31]	88	5 of 25	26 of 63	2.811	1.710	3.912	0.043	−
43 [31]	354	85 of 275	25 of 79	1.189	0.641	1.737	0.288	0
44 [31]	310	85 of 275	18 of 35	2.367	1.656	3.077	0.014	−

[a] Significant positive effect at $P < 0.1$ +; no significant effect 0; significant negative effect −.

has a prevalence of between 4 and 8% in the UK herd [1]. Used effectively meta-analyses can reduce a large amount of information from many trials to a manageable size, reducing the need for further field trials. They can also determine whether there is consistency between trials and explain discrepancies between findings [9]. This analysis combined data on approximately 2500 animals, considerably larger than any individual trial.

There are three main problems associated with the use of meta-analyses. Firstly, the studies used must be of satisfactory quality so that their findings are sufficiently robust for inclusion. Secondly the studies must be comparable with similar aims and differences that are

Table 4
Results from the final generalised estimating equation model of a multivariable analysis of the factors influencing the risk of RFM (Analysis 1)

Independent variable in the model	Odds ratio	Confidence intervals (95%)	*P*-value
Treatment with Vitamin E supplementation	0.47	0.33–0.66	<0.001
Parity[a]	1.47	0.86–2.50	0.154

Number of observations = 2495, number of groups (studies) = 23, Wald chi-squared (2) = 17.88 ($P < 0.001$).

[a] First calving or multiparous.

categorisable. These two problems were overcome in this analysis by setting clear selection criteria and identifying clear categories for comparison between studies (summarised in Table 2). The third problem is one of publication bias. In this analysis, further unpublished studies were sought to reduce this risk.

This analysis suggests that Vitamin E supplementation during the dry period in dairy cattle reduces the risk of RFM. Approximately half of the individual studies included in this paper showed a significant benefit of supplementation and inclusion of all studies in a multivariable model showed supplementation reduced the risk of RFM with an odds ratio of 0.47. However, the heterogeneity of odds ratios between studies means that such an overall odds ratio is not statistically valid. This heterogeneity also indicates that the response to Vitamin E supplementation is significantly influenced by the factors which varied between studies such as parity and breed, along with housing and feeding protocols. This is in agreement with previous risk analyses identifying parity [32], housing system [33] and breed [32] as influencing the prevalence of RFM. Unfortunately, due to the confounding effects of co-linearity, the management and cow factors included in this analysis could not be fully explored and thus a preferred management system could not be identified.

There are thought to be three reasons behind the aetiology of RFM; mechanical obstruction, failure of the myometrium to contract and failure of the feto-maternal union to separate [1]. It is hypothesised that 80% of cases of RFM are due to the failure of the feto-materal union to separate. Although the mechanisms associated with the separation of foetal and maternal tissues are poorly understood, there have been suggestions of insufficient leukocyte activity immediately post-partum resulting in inadequate collagen breakdown of the tissues and thus a failure of tissue separation [34]. Vitamin E supplementation has been shown to enhance various aspects of the immune system including enhanced migration and chemotaxis of polymorphonuclear cells [35] and increased chemotaxic responsiveness by blood neutrophils [7]. Vitamin E supplementation may reduce the prevalence of RFM through enhancement of the immune system and thus encourage tissue separation. RFM caused by either mechanical obstruction or failure of the myometrium to contract are probably not affected by antioxidant status. The different primary reasons behind RFM may explain the variation in findings reported in the trials included in this analysis.

Parity did not achieve statistical significance in the final multivariable model although there was a trend towards a higher risk in multiparous cows. Erb and Martin [32] previously reported an effect of parity, although in that study primiparous animals were at greater risk of RFM, possibly due to a higher incidence of dystocia and shorter gestation lengths in primiparous animals, both of which are risk factors for RFM. Reasons why multiparous animals may, however, be at a greater risk of RFM could be due to an increase in negative energy balance and hypocalcaemia, risk factors which are more common in multiparous animals [36]. No research has investigated why there might be such a difference in the response to Vitamin E supplementation with regards risk of RFM, between primi- and multiparous animals, although the cause of RFM (mechanical obstruction, etc.) may differ between age groups.

Table 5
Results from the final model of a multivariable analysis of the influence of type of Vitamin E supplementation on the risk of RFM

Independent variable in the model	Odds ratio	Confidence intervals (95%)	*P*-value
Natural compared with α-tocopherol acetate (synthetic)	0.53	0.27–1.02	0.059
Natural compared with α-tocopheryl acetate (synthetic)	0.49	0.24–0.99	0.047

This model included treated animals only (Analysis 2). Number of observations = 2558, number of groups (studies) = 40, Wald chi-squared (2) = 4.31 ($P = 0.116$).

There were significant differences between studies in supplementation protocol. Some studies used daily, in-feed supplementation while others used one off parenteral injections. In some cases selenium supplementation was used in addition to Vitamin E, in others Vitamin E supplementation alone was used. Careful classification of these factors prior to the meta-analysis allows factors to be included in the meta-analysis. Indeed a meta-analysis is an ideal way of assessing the importance of such factors.

When assessing the effects of supplementation protocol factors on those animals receiving Vitamin E, route and amount of Vitamin E were not significant. Due to co-linearity between type and timing of supplementation treatment, an ideal Vitamin E supplementation protocol could not be identified. This study found that the synthetic types of Vitamin E tended to be more effective than the natural compound in reducing the risk of RFM. This may be because synthetic Vitamin E tends to be more stable to environmental degradation than natural Vitamin E [37]. In the majority of studies (35/44, 80%) cows treated with vitamin E also received selenium. The level of selenium supplementation was found to have a significant effect on the response of RFM. Thus, it is possible that some of the apparent effects of Vitamin E may be actually related to selenium supplementation. Indeed one paper [13], data from which were included in our analysis, concluded that selenium alone was at least as effective as a combination of selenium and Vitamin E in reducing the incidence of RFM. However, from the data included in our analysis cattle supplemented with Vitamin E alone had 17% fewer cases of RFM than control cattle in the same studies ($P = 0.08$). Nevertheless this analysis has shown that there is currently insufficient published data to establish conclusively whether Vitamin E supplementation on its own is useful for the prevention of RFM.

In conclusion, this meta-analysis indicates a benefit of Vitamin E supplementation during the dry period on reducing the risk of RFM and that synthetic Vitamin E tends to be more effective than natural Vitamin E. However, because there were insufficient studies which evaluated the effect of Vitamin E alone on RFM, much of the apparent significant benefit of Vitamin E may be mediated by selenium. Also further work is required to assess the relative efficacies of different sources of Vitamin E, as no study to date has specifically compared synthetic and natural Vitamin E. Finally, the mechanism by which Vitamin E and/or selenium supplementation reduces the risk of RFM in dairy cows also needs to be determined.

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