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Publication Date

2021-08-13

Supplemental Material

<https://escholarship.org/uc/item/0h5330hv#supplemental>

Data Availability

The data associated with this publication are within the manuscript.

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Oral Ca supplementation in dairy cows: a protocol for a systematic review and meta-analysis

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Author Contributions: AV: Assist to develop search strategy and literature search, data screening, extraction, statistical analysis, and protocol and manuscript preparation. CBC and RBL: Data screening, review data extraction, review protocol and manuscript. EDF: Develop search strategy and literature search, edit protocol. NSDR: Assist, edit and review protocol and manuscript.

Amendments: Any amendments to this protocol will be documented and justified in the final review

Keywords: *calcium supplementation, dairy cow, milk yield, reproduction, oral calcium bolus*

INTRODUCTION

Rationale:

Transition cows face a sudden increase in nutrient requirements for milk production which challenges their homeostatic mechanisms at a time when dry matter intake and nutrient supply fall behind. When homeostatic mechanisms fail to cope with these increased requirements, metabolic diseases may occur. Hypocalcemia is one of these metabolic diseases, a consequence of cows' inability to replace the extracellular calcium used to produce colostrum and milk (Goff, 2008). Clinical hypocalcemia is identified by US producers in 2.8% of the cows (USDA-NAHMS, 2014a). However, subclinical hypocalcemia prevalence in multiparous cows is much higher ($\approx 50\%$; Reinhardt et al., 2011). Subclinical hypocalcemia has been associated with increased risk of disease and impaired reproductive function (Ribeiro et al., 2013; Caixeta et al., 2017; Rodríguez et al., 2017). Controversially, subclinical hypocalcemia's association with milk yield is unclear (Østergaard and Larsen, 2000; Chapinal et al., 2012; Jawor et al., 2012), likely because the degree of hypocalcemia, as well as, the timing of the condition (day postpartum and duration) may play a role (McArt and Neves, 2020).

Peripartum calcium supplementation (injectable or oral) to prevent hypocalcemia, is a management strategy implemented in 69% of US dairy herds (USDA-NAHMS, 2014b). Oral calcium supplementation has been proposed by some authors as the recommended approach for cows that are standing but may suffer from hypocalcemia (Oetzel, 2013), based on the premise that providing large amounts of highly soluble calcium forms creates a high concentration gradient between the digestive tract and extracellular fluids, leading to the passive absorption of

ionized calcium (Goff, 2018). Oral calcium can be administered as liquid, paste, gel, or bolus; nevertheless, boluses are preferred due to their reduced risk of aspiration compared to the other forms (Oetzel, 2013). Over the last 10 years, studies have been conducted to assess long term implications of postpartum oral calcium supplementation as boluses on dairy cows. These studies observed minimal treatment effects at a group level, and suggest that productive and health responses to oral calcium supplementation are conditional to cow-level factors, which also influence the direction of that response (Oetzel and Miller, 2012; Martinez et al., 2016b; Leno et al., 2018). Currently, a systematic review or meta-analysis on the effect of oral calcium supplementation on productive and reproductive outcomes is lacking. Results from the proposed study may help to orientate further research and to support management related decisions in commercial farms where oral calcium supplementation is implemented.

Objectives:

The objective of this protocol is to specify the method for a systematic review and meta-analysis to address the following research question: Is postpartum oral calcium supplementation associated with production or reproduction performance in dairy cows?

- a) Population: dairy cows
- b) Intervention: oral calcium supplementation, oral calcium supplement, calcium supplement, oral calcium, calcium bolus, calcium drench, calcium paste, calcium gel, calcium suspension, calcium drink, calcium infusion.
- c) Comparator: placebo or no oral calcium supplementation
- d) Outcomes: milk yield, milk production, milk, energy-corrected milk, milk protein, milk fat, somatic cell count, pregnancy to first service, pregnancy to first artificial insemination, pregnancy to first AI, pregnancy to 1st service, pregnancy to 1st AI, pregnancy to 1st artificial insemination, conception to first artificial insemination, conception to first AI, conception to 1st service, conception to 1st AI, conception to 1st artificial insemination.

METHODS

Eligibility criteria: As the research question, the eligibility criteria were defined based on the PICO elements.

- Study design, characteristics, and population. The systematic review will include primary research studies, including non-randomized and randomized controlled trials, which are available in English. Observational studies will be excluded. Eligible studies must have investigated postpartum oral calcium supplementation in dairy cows. Only peer reviewed studies will be considered. No restriction on publication date will be applied.

- Intervention and comparator groups. Eligible studies must have evaluated oral calcium supplementation, with no restriction for oral calcium type, dose, or supplementation duration. The oral calcium supplementation must have been compared to no intervention or placebo. Studies evaluating a combined source of calcium and energy will be excluded.

- Outcome measures. Studies must include at least one main productive (milk yield, milk production, milk) or reproductive outcome (pregnancy to first service, pregnancy to first artificial

insemination, pregnancy to first AI, pregnancy to 1st service, pregnancy to 1st AI, pregnancy to 1st artificial insemination, conception to first artificial insemination, conception to first AI, conception to 1st service, conception to 1st AI, conception to 1st artificial insemination).

Information sources: After consultation with an experienced health and veterinary science academic librarian (EDF), the following electronic databases will be searched: Biosis (Web of Science, 1926 to present), CAB Abstracts (CAB Direct, 1973 to present), Medline (PubMed, 1966 to present), and Scopus (Scopus, 1996 to present). The bibliography of relevant studies will be hand-searched by the first author.

Search strategy: The search strategy will be designed with the assistance of an academic librarian (EDF). For the preliminary search described in Appendix 1 and conducted in May 2021, the first author selected key words from relevant literature and five papers to be used to calibrate the search (Appendix 2). Subject headings or keywords were mined by finding these references in PubMed and Cab Direct. Keywords were collected and compared with keywords already utilized. And Yale MeSH analyzer was also utilized to compare common Medical Subject Headings across articles.

Systematic review software utilized: Endnote (Clarivate) for deduplication, Covidence for title/abstract screening and full text screening, and Zotero for full text beta retrieval in Covidence.

APPENDIX 1: Complete search strategy

Databases and Interfaces Searched:

Database	Interface	Date Coverage	Date Searched
CAB Abstracts [Included products: CAB ABSTRACTS, VetMed Resource, CABI Full Text, Global Health, Animal Health and Production Compendium (AHPC)]	CAB Direct	1973 to Present	13 May 2021
Medline (Included products: Medline, in process citations, "ahead of print" citations, out-of-scope citations, journals indexing prior to medline inclusion, pre-1966 citations, PubMed Central, author manuscripts NIH funding, NCBI Bookshelf)	PubMed	1902 to Present	13 May 2021
Scopus	Scopus	1996 to Present	13 May 2021
Biosis	Web of Science	1926 to Present	13 May 2021

Search Database: CAB Direct

Search ID	Terms	Results
#1	od:("cattle" OR "Holstein-Friesian" OR "Holstein (cattle breed)" or "Simmental" OR "Jersey (cattle breed)" OR "American Brown Swiss" or "Ayrshire" or "Guernsey (cattle breed)") OR de:("cows" OR "dairy cows") OR up:("bos") OR ti:("cow" OR "cattle" OR "holstein-friesian" OR "holstein" OR "jersey" OR "cows" OR "heifer" OR "heifers" OR "simmental" OR "ayrshire" OR "guernsey" OR "brown swiss" OR "B. taurus" OR "B. Indicus" OR "bos") OR ab:("cow" OR "cows" OR "heifer" OR "heifers" OR "cattle" OR "holstein-friesian" OR "holstein" OR "simmental" OR "jersey" OR "ayrshire" OR "guernsey" OR "brown swiss" OR "B. taurus" OR "B. Indicus" OR "bos")	630,823

#2	(de:(“calcium” or "calcium chloride" OR "calcium carbonate" OR "calcium propionate" OR "calcium sulfate" OR "calcium sulphate")) OR (ti:(“oral calcium” or “calcium supplement*”)) OR (ab:(“oral calcium” or “calcium supplement*”))	145,513
#3	de:(“pregnancy” OR “parturition” OR “reproduction” OR “calving” OR “reproductive performance” OR “postpartum period”) OR ID:(“gestation” OR “pregnancy”) OR ti:(“pregnan*” OR “gestat*” OR “postpartum” OR “post-partum”) OR ab:(“pregnan*” OR “gestat*” OR “postpartum” OR “post-partum” OR “calving” OR “early-lactation” OR “early lactation”)	403,362
#4	de:(“hypocalcaemia” OR “mineral metabolism disorders”) OR ID:(“hypocalcemia” OR “milk fever”) OR ti:(“hypocalc*” OR “milk fever”) OR ab:(“hypocalc*” OR “milk fever”)	7,514
#5	de:(“milk production” OR “milk yield”) OR ti:(“milk yield” OR “milk production”) OR ab:(“milk yield” OR “milk production”)	102,565
#6	#3 OR #4 OR #5	482,329
#7	#1 AND #2 AND #6	3,995
#8	#7 AND Filters[English] AND Filters[Article]	2,354

Search Database: PubMed

Search ID	Terms	Results
#1	“cow”[tiab] OR “cows”[tiab] OR “heifer”[tiab] OR “heifers”[tiab] OR “cattle”[tiab] OR “holstein-friesian”[tiab] OR “holstein”[tiab] OR “simmental”[tiab] OR “jersey”[tiab] OR “ayrshire”[tiab] OR “guernsey”[tiab] OR “brown swiss”[tiab] OR “B. taurus”[tiab] OR “B. Indicus”[tiab] OR “bos”[tiab] OR “cattle”[mesh]	399,129
#2	"Calcium, Dietary"[Mesh] OR “calcium supplement”[tiab] OR “calcium supplements”[tiab] OR “oral calcium”[tiab] OR “calcium supplementation”[tiab] OR “calcium bolus”[tiab] OR “calcium administration”[tiab] OR "Calcium/administration and dosage"[Mesh] OR "Calcium Chloride/administration and dosage"[Mesh]	22,712

	dosage"[Mesh] OR "Calcium Sulfate/administration and dosage"[Mesh] OR "Calcium Carbonate/administration and dosage"[Mesh] OR "calcium propionate" [Supplementary Concept]	
#3	"Pregnancy"[Mesh] OR "Reproduction"[Mesh] OR "Postpartum Period"[Mesh] OR "Parturition"[Mesh] OR "pregnant"[tiab] OR "postpartum"[tiab] OR "reproductive"[tiab] OR "post-partum"[tiab] OR "calving"[tiab] OR "early-lactation"[tiab] OR "early lactation"[tiab]	1,337,451
#4	"Hypocalcemia"[Mesh] OR "hypocalcemia"[tiab] OR "Milk Fever"[tiab]	15,245
#5	NOT ("clinical conference"[Publication Type] OR "review"[Publication Type] OR "editorial"[Publication Type] OR "pubmed books"[Filter] OR "case reports"[Publication Type])	
#6	#3 OR #4	1,351,064
#7	#1 AND #2 AND #6	296
#8	#7 NOT #5	269
#9	#8 AND AND (english[Filter])	247

Search Database: Biosis

Search ID	Terms	Results
#1	TOPIC: ("cow" OR "heifer" OR "heifers" OR "cattle" OR "holstein-friesian" OR "holstein" OR "jersey" OR "simmental" OR "ayrshire" OR "guernsey" OR "brown swiss" OR "B. taurus" OR "B. Indicus" OR "bos" OR "cows")	358,527
#2	TOPIC: ("calcium chloride" OR "calcium carbonate" OR "calcium propionate" OR "calcium sulfate" OR "calcium sulphate" OR "calcium bolus") OR TOPIC: ("oral calcium" OR "calcium supplement*" OR "calcium administration")	37,862
#3	TOPIC: ("pregnan*" OR "gestat*" OR "postpartum" OR "post-partum" OR "calving" OR "early-lactation" OR "early AND	516,793

	lactation”)	
#4	TOPIC: (hypocalc* OR "milk fever")	10,720
#5	TOPIC: (“milk yield” OR “milk production”)	37,831
#6	#3 OR #4 OR #5	553,634
#7	#1 AND #2 AND #6	162
#8	#7 AND English AND Article	116

Search Database: Scopus

Search ID	Terms	Results
#1	TITLE-ABS-KEY ("cow" OR “cows” OR "cattle" OR "holstein-friesian" OR "holstein" OR "jersey" OR "simmental" OR "ayrshire" OR "guernsey" OR "brown swiss" OR "B. taurus" OR "B. Indicus" OR "bos" OR "cows")	540,249
#2	((TITLE-ABS-KEY ("calcium chloride" OR "calcium carbonate" OR "calcium propionate" OR "calcium sulfate" OR "calcium sulphate" OR "calcium bolus") OR TITLE-ABS-KEY ("oral calcium" OR "calcium supplement*" OR "calcium administration"))	100,305
#3	TITLE-ABS-KEY (“pregnan*” OR “gestat*” OR “postpartum” OR “post-partum” OR “calving” OR “early-lactation” OR “early AND lactation”)	56,977
#4	TITLE-ABS-KEY (hypocalc* OR "milk fever")	29,669
#5	TITLE-ABS-KEY (“milk AND yield” OR “milk AND production”)	51,198
#6	#3 OR #4 OR #5	128,124
#7	#1 AND #2 AND #6	218

#8	#7 AND English AND Article	168
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Total Records	Total Records after deduplication	Deduplication software/methodology
3030	2577	EndNote
2577	2515	Covidence

APPENDIX 2: Calibration articles

Article Citation:
Domino, A.R., H.C. Korzec, and J.A.A. McArt. 2017. Field trial of 2 calcium supplements on early lactation health and production in multiparous Holstein cows. <i>J. Dairy Sci.</i> 100:9681–9690. doi:10.3168/jds.2017-12885.
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Oetzel, G.R., and B.E. Miller. 2012. Effect of oral calcium bolus supplementation on early-lactation health and milk yield in commercial dairy herds. <i>J. Dairy Sci.</i> 95:7051–7065. doi:10.3168/jds.2012-5510.
Valdecabres, A., and N. Silva-del-Río. 2020. Effects of postpartum oral calcium supplementation on milk yield, milk composition and reproduction in multiparous Jersey and Jersey × Holstein crossbreed cows. <i>J. Dairy Sci.</i> doi:10.3168/jds.2020-19079.

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