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Effects of a single transdermal administration of flunixin meglumine in early postpartum Holstein Friesian dairy cows: Part 2. Milk yield, culling risk, and reproductive performance

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ABSTRACT

This study was conducted to assess the effects of a single transdermal administration of flunixin meglumine (FM) in early postpartum Holstein Friesian dairy cows on milk yield, culling risk, and reproductive performance. We hypothesized that FM treatment would reduce systemic inflammation, leading to higher milk yield, reduced culling risk, and better reproductive performance in the subsequent lactation. Holstein Friesian dairy cows [n = 500, 153 primiparous (PRIM), 347 multiparous (MULT)] from 3 farms in northeast Germany were enrolled in a prospective, randomized controlled clinical trial. Farms at risk for cows with excessive postpartum inflammation were identified in a preliminary trial by measuring serum haptoglobin concentrations in their fresh lactating cows. Only cows that had a eutocic birth and delivered a singleton calf alive, with no signs of milk fever or retained fetal membranes and rectal temperature ≤40°C at first clinical examination, were included within 24 to 36 h postpartum. Treatment included a single transdermal administration of either FM (3.33 mg/kg) or a placebo as control (CON). Milk production, milk solids, urea, and somatic cell count were recorded monthly for 8 mo after calving. Culling risk, first-service conception risk, and days open were retrieved from the farms' herd management software. Separate models for PRIM and MULT cows were built for most parameters because of significant effects of parity and parity × treatment interaction. Energy-corrected milk yield from 8 monthly Dairy Herd Improvement-equivalent tests was slightly greater in PRIM cows treated with FM (29.51 and 30.73 ± 1.35 kg, CON vs. FM), whereas it was reduced in treated MULT cows (38.23 and 37.47 ± 1.17 kg, CON vs. FM) compared with CON. Milk fat and protein yields were greater in FM-treated PRIM cows and lower in treated MULT cows compared with CON. Milk urea and somatic cell count were not affected by treatment. No differences in culling risk, first-service conception risk, or days open were observed. We conclude that a single transdermal administration of FM in early postpartum dairy cows on farms at risk for excessive postpartum inflammation slightly increased milk, milk fat, and milk protein yields in PRIM cows and decreased these variables in MULT cows. Neither culling risk nor fertility was affected by treatment in this study.
Key words: transition dairy cow, flunixin meglumine, milk yield, reproductive performance

INTRODUCTION

Dairy cows are especially prone to clinical diseases within the first 2 wk after parturition (Goff and Horst, 1997). This has been attributed to profound metabolic adaptations to lactation (Bell, 1995; Horst et al., 2005) including a period of negative energy balance (Drackley, 1999). Variable degrees of stressors intrinsic to the calving process itself [e.g., stress (Chebel et al., 2016; Nagel et al., 2016), dystocia and pain (Vannucchi et al., 2015), tissue lesions (Vieira-Neto et al., 2016), and bacterial contamination of the uterus (Sheldon et al., 2002)] can further exacerbate the situation. In addition to clinical diseases, subclinical metabolic disorders such as subclinical hypocalcemia (Reinhardt et al., 2011; Venjakob et al., 2017) and ketosis (McArt et al., 2012) are varyingly prevalent in dairy herds and interrelated (Rodríguez et al., 2017). The detrimental consequences of different transition cow disorders on subsequent milk yield (**MY**), culling risk, reproductive performance, and, hence, the economic efficiency of dairy farms, have been outlined by numerous researchers and reviewed by Roche et al. (2013).

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To different extents, immune activation and systemic inflammation have been shown to be associated with all of the aforementioned diseases and have therefore become an intensely discussed issue in the bovine over the past decades (Horst et al., 2021; Bradford and Swartz, 2020). Although traditional dogma regards inflammation as an important feature in the elimination of invading pathogens, inflammatory processes can exceed a physiological level and result in unnecessary collateral damage to host tissues and reduced nutrient availability, leading to exacerbated negative energy balance and metabolic dysregulation (Bertoni et al., 2008; Sordillo et al., 2009; Bradford and Swartz, 2020). Therefore, a growing body of research has assessed different approaches to mitigate systemic inflammation after calving, including treatment of periparturient dairy cows with nonsteroidal anti-inflammatory drugs (**NSAID**). However, treatment effects of NSAIDs on MY, culling risk, and reproductive performance have been inconsistent.

Acetylsalicylate acid (**ASA**) treatment early after parturition increased MY of dairy cows in several (Bertoni et al., 2004; Farney et al., 2013b; Carpenter et al., 2016; Barragan et al., 2020a,b) but not all studies (Barragan et al., 2020b). In 2 studies (Bertoni et al., 2004; Farney et al., 2013b), multiparous (**MULT**) cows treated with ASA were more likely to develop metritis. Conversely, other authors reported a lower risk for clinical metritis (Barragan et al., 2021) and a higher first-service conception risk (**FSCR**) and fewer days open (**DO**; Barragan et al., 2020a; Bertoni et al., 2004) in ASA-treated cows compared with controls. Overall, culling risk was not affected by ASA treatment. Meloxicam treatment early after parturition increased MY in some studies (Carpenter et al., 2016; Shock et al., 2018; Swartz et al., 2018), whereas other authors reported no effect on MY (Newby et al., 2013a; Mainau et al., 2014; Pascottini et al., 2020). Neither fertility (Carpenter et al., 2016) nor endometrial cytology (Pascottini et al., 2020) was affected by meloxicam treatment. Two articles described a reduced culling risk for meloxicam-treated cows compared with controls (Carpenter et al., 2016; Shock et al., 2018). Carprofen treatment early after parturition increased 305-d MY in primiparous (**PRIM**) cows (Stilwell et al., 2014), but had no effect on MY in 2 other studies (Meier et al., 2014; Giammarco et al., 2016). However, Giammarco et al. (2016) reported a lower culling risk and higher FSCR in cows treated with carprofen, whereas Stilwell et al. (2014) found greater DO in carprofen-treated cows compared with controls, and Meier et al. (2014) did not observe any treatment effects. Treatment of early postpartum cows with ketoprofen failed to show any effects on MY, reproductive performance, or culling risk (Richards et al., 2009; Kovacevic et al., 2018). Early lactation MY was not affected by postpartum treatment with flunixin meglumine (**FM**) in 2 studies (Shwartz et al., 2009; Giammarco et al., 2016). Although FM treatment within 12 h after calving decreased culling risk and enhanced fertility in one study (Giammarco et al., 2016), FM treatment before or directly after parturition increased the odds of stillbirth and retained fetal membranes, respectively, in 2 other studies (Waelchli et al., 1999; Newby et al., 2017).

Treatment of early postpartum dairy cows with an NSAID can be considered a tool to mitigate systemic inflammation, thereby enhancing the cows' resilience and immunity and improving productive performance. However, many factors (e.g., pharmaceutical agent, dosage, time of first administration, single vs. multiple administrations) seem to determine treatment efficiency. This study was designed to assess the effects of a single transdermal administration of FM within 24 to 36 h after calving on MY, culling risk, and reproductive performance in subsequent lactation. In a companion article, we reported the treatment effects on inflammatory and metabolic markers in blood, uterine health, and indicators of pain (Schmitt et al., 2023). The hypothesis of the present study was that FM-treated cows would show increased MY, reduced culling risk, and improved reproductive performance due to the anti-inflammatory and antipyretic treatment effect. To prevent negative effects reported previously, we included only clinically healthy cows with no signs of retained fetal membranes in this study.

MATERIALS AND METHODS

The Institutional Animal Care and Use Committee of the Free University of Berlin and the Federal State Office of Occupational Safety, Consumer Protection and Health revised and approved the experimental procedures described below (animal care protocol number: 2347–10–2018).

Animals and Farms

A total of 500 Holstein Friesian dairy cows (n = 153 PRIM, n = 347 MULT) were enrolled in this trial from November 2018 to November 2019. Detailed descriptions of farms (n = 3), housing, and pre- and early postpartum diets are described in the companion article (Schmitt et al., 2023). Briefly, all farms were located in northeast Germany and kept ≥1,000 milking cows in freestall barns with cubicles. During the prepartum period, all cows were housed in group pens with deep straw bedding. All cows were offered a TMR and milked twice daily in either a herringbone (farms 1

and 2) or parallel (farm 3) milking parlor. Farms were chosen for this study because a sample (n = 10) of fresh lactating cows from all 3 farms had expressed excessive postpartum inflammation through elevated mean serum haptoglobin (**HP**) concentrations (>0.6 g/L), as described in a preliminary trial (Schmitt et al., 2021).

Sample Size Calculation

Sample size calculation for this study was based on a minimum difference of 1.31 g/L in serum HP concentration on d 6 postpartum between cows treated with FM and cows that remained untreated (Schmitt et al., 2023). Using a post hoc power analysis, we determined that we would be able to detect ($\alpha = 0.05$, $\beta = 0.80$) a 1.8-kg difference in milk yield at first test (SD: 8 kg) and a 10.5-percentage-unit difference in pregnancy per AI to first postpartum service, when pregnancy per AI of control cows was 30%, between FM and control cows with the 250 cows per group in our study.

Treatment Allocation

Cows were considered eligible for enrollment when they had a eutocic birth (scores 1 and 2; Schuenemann et al., 2011) with an alive singleton calf 24 to 36 h before first clinical examination (d 2 postpartum). Cows were excluded from the trial if they had rectal temperature (**RT**) >40°C or displayed clinical signs of retained fetal membranes (**RFM**) or milk fever (**MF**). A cow was considered to have MF when typical signs of hypocalcemia were observed (i.e., weakness or weight shifting, muscle tremors, sternal or lateral recumbency, decreased gastrointestinal activity, rapid heart rate, weak pulse, decreased RT) within 72 h after parturition (Kelton et al., 1998). When fetal membranes were visible at the vulva more than 24 h after the first observation of the cow following parturition, the cow was diagnosed with RFM (Kelton et al., 1998).

Treatment

Cows were treated once between 24 and 36 h postpartum with either Finadyne Transdermal (flunixin meglumine, 83 mg/mL, levomenthol, 50 mg/mL, Allura Red AC (E129), 0.2 mg/mL; MSD Animal Health; FM] at a dose of 3.33 mg/kg or a placebo [Allura Red AC (E129), 0.2 mg/mL in PBS; MSD Animal Health; **CON**]. The respective fluid was poured on the skin over the dorsal line of vertebrae along the back of the cow according to the manufacturer's instructions. Finadyne Transdermal is approved for the treatment of bovine respiratory disease, acute mastitis, interdigital phlegmon, interdigital dermatitis, and digital dermatitis. This study involved an extra-label use to reduce parturition-induced inflammation in fresh lactating cows.

Blinding and Randomization

To blind farm personnel, the investigating veterinarian (R. Schmitt), and researchers performing statistical analyses to treatment, bottle labels of treatment and placebo were covered with nontransparent tape and numbered in alternating order by a study-independent person. Cows were blocked by parity (1 and ≥2). Within PRIM and MULT cows, respectively, treatment was randomized through alternating treatment using even and odd bottle numbers, respectively. Hence, every other cow received FM treatment (FM group, n = 250), and the remaining cows received placebo (CON group, n = 250).

Recording of Health Events and Supportive Therapy

Trained farm personnel examined cows daily throughout the first 10 DIM, assessing changes in MY, RT, visual assessment of vaginal discharge, and signs of dehydration (e.g., sunken eyes) and depression (e.g., reduced general appearance, decreased appetite, poor rumen fill). Rectal palpation, abdominal and cardiovascular auscultation, and blood or urine testing for BHB concentration was additionally performed when cows displayed any symptoms of disease. Transition diseases were defined as reported in Schmitt et al. (2023).

All cases of clinical disease were treated according to common protocols in accordance with the local veterinarian. Within the first 15 DIM, treatment with an NSAID or an antibiotic alone or both due to clinical signs of disease that required medication (e.g., high fever, sunken eyes, dullness, anorexia, poor rumen fill, fetid discharge, or severe mastitis) was considered a supportive therapy, which was documented, but the cows were not excluded from subsequent data collection.

Data Collection

Milk volume, fat, protein, urea, and SCC were assessed once per month during routine milk recordings (German equivalent to DHI testing by the federal milk control association LKV, Berlin-Brandenburg, Germany) for 8 mo after calving. The results were collected from on-farm computer records (HERDEplus, dsp-Agrosoft Ltd.).

Data regarding removal from the herd (i.e., by death, slaughter, or selling) and reproductive performance (i.e., FSCR, DO), respectively, were obtained from the

herd management software as mentioned above. Culling events were collected from enrollment in the study until 60 DIM. Cows were considered culled during the postpartum period if they were removed from the herd at ≤60 DIM, except for sales for dairy purposes.

Statistical Data Analyses

Individual cow data (e.g., calving date, parity, treatment allocation, clinical data) were collected in Excel (Office 2013; Microsoft Deutschland Ltd.) during the trial. All data pertaining to MY, reproductive performance, and culling risk were later transferred from HERDEplus to Microsoft Excel. Statistical analyses were performed using SPSS for Windows (version 26.0; IBM Corp.).

Treatment Effect on MY, Milk Composition, and SCC. Energy-corrected milk yield was calculated using the following formula: ECM = {milk (kg) × [(0.38 × milk fat (%)] + [0.21 × milk protein (%)] + 1.05}/3.28 (Spiekers and Potthast, 2004). The SCC was log-transformed into a linear score (**LS**) as [ln (SCC/100)/ln (2)] + 3 (Ali and Shook, 1980). All continuous data regarding MY and milk composition (i.e., monthly ECM, fat, protein, urea, and LS) were tested for normality using the Kolmogorov-Smirnov test and graphical methods (histograms, Q-Q plots). During the model building process, each variable's residuals were assessed for heteroscedasticity and normality. Monthly ECM and milk components were not normally distributed; therefore, data were logarithmically transformed and Akaike's information criterion (AIC) was used to determine whether model fit was improved. Model fit and normality of residuals were acceptable (based on AIC and graphical assessment) for monthly ECM, fat, protein, urea, and LS.

To evaluate the effects of FM treatment on monthly ECM, milk components, and LS, generalized linear mixed regression models were built using the GENLINMIXED procedure of SPSS. Monthly ECM, fat, protein, urea, and LS were considered the outcome variables, and the predictor variables included in the initial model were treatment, time (test-day number), parity, and their interactions. The model accounted for repeated measurements (with first-order autoregressive covariance structure) and a hierarchical data structure (cow within herd), where cow was the experimental unit and farm was considered a random effect.

Evaluation of Treatment Effect on Culling Risk and DO. To assess the effect of the treatment on the proportion of cows culled by 60 DIM and the proportion of cows pregnant by 200 DIM, a survival analysis was performed using Kaplan-Meier survival analysis and a Cox proportional hazard analysis. The final model accounted for herd as a random effect and cluster-specific correlations (shared frailty term; cows within farm). The outcome variable was the probability of the respective event (culling and diagnosed pregnancy) per unit of time (the median DIM at which cows were culled and diagnosed pregnant, respectively, was calculated). Cows that left the herd due to culling or death within 200 DIM were right-censored from the model for time to diagnosed pregnancy. Treatment, parity, and time to first insemination were included as fixed effects. Proportional hazards assumption was graphically assessed by plotting the –ln [–ln(survival)] curves for FM and CON cows against the ln(survival time). The proportional hazards assumption was assumed to be met when the lines were approximately parallel. Frailty models were fitted in R version 4.0.2 (https://www.r-project.org/) using the R package coxme (version 2.2-16). Survival curves were plotted using the package survminer (version 0.4.8).

Evaluation of Treatment Effect on FSCR. To evaluate the effect of the treatment on FSCR, the variable was dichotomized as follows: cows were classified into 0 (= did not conceive at first service) and 1 (= diagnosed pregnant to first AI). A binary logistic regression model was built using the GENLINMIXED procedure as described above. Farm was considered a random effect, and treatment and parity were included as fixed effects. Time to first insemination was included as a covariate.

Influence of Parity

Whenever a significant treatment × parity interaction was observed, separate models were calculated for PRIM and MULT cows. In the separate models for MY, age at first calving and 305-d MY from the previous lactation were included as covariates for PRIM and MULT cows, respectively.

Data Presentation and Level of Significance

Data are presented as least squares means ± standard errors of the mean unless otherwise indicated. Effects were considered significant if $P < 0.05$ and tendencies were declared at $0.05 \leq P \leq 0.10$.

RESULTS

A total of 500 cows (153 PRIM, 347 MULT) were enrolled. The initial distribution of time from calving to treatment, lactation number, and clinical and laboratory parameters was not significantly different between the treatment groups (Schmitt et al., 2023). Within the first 15 DIM, 3 multiparous cows died from acute meta-

Table 1. Descriptive statistics (mean ± SD) of milk yield (MY), milk components, and SCC from 8 monthly milk recordings after calving for primiparous (PRIM) and multiparous (MULT) cows on 3 farms

Milk recording (8 mo)	Farm 1		Farm 2		Farm 3	
	PRIM	MULT	PRIM	MULT	PRIM	MULT
Sample size,[1] no.	34	106	51	53	26	76
MY, kg	28 ± 6	37 ± 9	33 ± 6	40 ± 9	31 ± 5	37 ± 8
ECM, kg	28 ± 5	37 ± 8	33 ± 6	39 ± 9	30 ± 4	36 ± 6
Milk fat, %	4.0 ± 0.5	4.0 ± 0.6	3.8 ± 0.7	4.0 ± 0.9	3.8 ± 0.5	3.9 ± 0.6
Milk fat, kg	1.1 ± 0.2	1.5 ± 0.4	1.3 ± 0.3	1.6 ± 0.4	1.1 ± 0.2	1.4 ± 0.3
Milk protein, %	3.5 ± 0.3	3.5 ± 0.3	3.3 ± 0.3	3.3 ± 0.3	3.4 ± 0.3	3.4 ± 0.3
Milk protein, kg	1.0 ± 0.2	1.3 ± 0.3	1.1 ± 0.2	1.3 ± 0.3	1.0 ± 0.1	1.2 ± 0.2
Milk urea, mmol/L	233 ± 41	222 ± 40	230 ± 38	235 ± 40	233 ± 58	250 ± 64
SCC, $\times 10^3$ cells/mL	95 ± 172	249 ± 751	269 ± 859	261 ± 695	127 ± 452	204 ± 613
SCC (LS)[2]	2.0 ± 1.4	2.6 ± 1.9	2.4 ± 2.0	2.9 ± 1.9	1.5 ± 1.6	2.1 ± 2.1

[1]Sample size is the total number of cows included in statistical analyses for 8 monthly milk recordings.
[2]SCC was converted into a linear score (LS) by log-transformation.

bolic disorders (CON = 1, FM = 2, respectively). A total of 30 versus 24 cows were supportively treated with NSAID in the CON and FM groups, respectively ($P = 0.39$). Supportive antibiotic treatment was performed in 24 CON and 20 FM cows ($P = 0.53$). Combined therapy (NSAID and an antibiotic) was performed in 17 CON versus 15 FM cows ($P = 0.72$).

MY, Milk Composition, and SCC from 8 Monthly DHI-Equivalent Tests

Data from DHI testing were included from 6 to 280 DIM. Some individual cow data were missing (e.g., because data transfer from the milking parlor failed or the cow had already been culled or dried off). Therefore, a total of 405, 423, 407, 386, 370, 360, 349, and 332 cows were assessed in milk recording number 1, 2, 3, 4, 5, 6, 7, and 8 postpartum, respectively. The overall mean DIM ± standard deviation was 28 ± 19, 65 ± 20, 98 ± 20, 134 ± 17, 165 ± 17, 196 ± 16, 227 ± 16, and 260 ± 19 for milk recording number 1, 2, 3, 4, 5, 6, 7, and 8, respectively. Descriptive statistics of MY, milk components, SCC, and LS of PRIM and MULT cows from all 3 farms over the study period are given in Table 1. With both parities combined in the model, treatment had no effect on monthly ECM (33.67 and 33.74 ± 0.9 kg for CON vs. FM, respectively; Table 2). Significant effects of parity ($P < 0.01$) and time ($P < 0.01$), as well as interactions of time × parity ($P < 0.01$) and treatment × parity ($P < 0.01$) were observed (Table 2). In the separate model, PRIM cows treated with FM showed higher ECM yields (29.51 and 30.73 ± 1.35 kg for CON vs. FM, respectively, $P < 0.01$; Table 3, Figure 1A). In MULT cows, the treatment effect was reversed, as CON cows produced more ECM (38.23 and 37.47 ± 1.17 kg for CON vs. FM, respectively; $P < 0.01$; Table 3, Figure 1B).

Milk fat content (kg) was influenced by time ($P < 0.01$) and parity ($P < 0.01$), and significant treatment × parity ($P = 0.01$) and time × parity ($P < 0.01$) interactions were observed (Table 2). The separate model revealed higher milk fat yields in PRIM cows treated

Table 2. Results of the generalized linear mixed model assessing the effects of placebo (CON) and flunixin meglumine (FM) treatment on milk yield, milk components, and SCC from 8 monthly DHI-equivalent tests

Variable	Treatment[1]		SEM	*P*-value[2]					
	CON	FM		Trt	T	Par	Trt × T	Trt × Par	T × Par
ECM, kg	33.67	33.74	0.94	0.78	<0.01	<0.01	0.72	<0.01	<0.01
Milk fat, kg	1.32	1.33	0.05	0.53	<0.01	<0.01	0.67	<0.01	<0.01
Milk fat, %	3.87	3.92	0.06	0.13	<0.01	0.15	0.89	0.50	0.77
Milk protein, kg	1.15	1.15	0.02	0.96	<0.01	<0.01	0.65	<0.01	<0.01
Milk protein, %	3.37	3.37	0.04	0.75	<0.01	<0.01	0.85	0.26	0.25
Milk urea, mmol/L	233.7	233.2	4.4	0.81	<0.01	0.03	0.96	0.12	0.69
SCC, LS[3]	2.34	2.33	0.24	0.97	<0.01	<0.01	0.92	0.77	<0.01

[1]Treatment consisted of 1 transdermal administration of flunixin meglumine (83 mg/mL) at a dose of 3.33 mg of flunixin/kg of BW (FM group; n = 250) or placebo as control (CON group; n = 250).
[2]Trt = treatment; T = time; Par = parity.
[3]SCC was converted into a linear score (LS) by log-transformation.

Table 3. Results of the separate generalized linear mixed models[1] evaluating the effect of placebo (CON) and flunixin meglumine (FM) treatment on ECM, milk fat, and milk protein from 8 monthly DHI-equivalent tests for primiparous (PRIM) and multiparous (MULT) cows

	PRIM						MULT					
	Treatment[2]			*P*-value[3]			Treatment			*P*-value		
Variable	CON	FM	SEM	Trt	T	Trt × T	CON	FM	SEM	Trt	T	Trt × T
ECM, kg	29.54	30.73	1.35	<0.01	0.16	0.96	38.23	37.47	1.17	<0.01	<0.01	0.34
Milk fat, kg	1.15	1.21	0.06	<0.01	0.82	0.92	1.51	1.48	0.06	0.03	<0.01	0.26
Milk protein, kg	1.02	1.05	0.04	<0.01	<0.01	0.89	1.30	1.27	0.03	0.01	<0.01	0.36

[1]Age at first calving and 305-d milk yield from the previous lactation were included as covariates for PRIM and MULT, respectively ($P < 0.01$).
[2]Treatment consisted of 1 transdermal administration of flunixin meglumine (83 mg/mL) at a dose of 3.33 mg of flunixin/kg of BW (FM group; n = 75 primipara, n = 175 multipara) or placebo (CON group; n = 78 primipara, n = 172 multipara).
[3]Trt = treatment; T = time.

with FM compared with CON (1.15 and 1.21 ± 0.06 kg for CON and FM, respectively; $P = 0.01$); Table 3). In MULT cows treated with FM, lower milk fat yields compared with CON cows were observed (1.51 and 1.48 ± 0.06 kg for CON and FM, respectively; $P = 0.03$). Relative milk fat content (%) was not influenced by treatment (Table 2).

In the combined model, milk protein content (kg) was affected by time ($P < 0.01$) and parity ($P < 0.01$), and significant interactions of treatment × parity ($P < 0.01$) and time × parity ($P < 0.01$) were found. The separate model showed higher milk protein yields in FM-treated PRIM cows compared with CON (1.02 vs. 1.05 ± 0.04 kg for CON and FM, respectively; $P < 0.01$; Table 3). Multiparous cows treated with FM had lower milk protein yields compared with CON (1.30 and 1.27 ± 0.03 kg for CON and FM, respectively; $P = 0.01$; Table 3). No treatment effect on relative milk protein content (%) was observed (Table 2).

Milk urea content was influenced by time ($P < 0.01$) and parity ($P = 0.03$) (Table 2). No effect of treatment ($P = 0.81$) was observed. Linear score was not different between treatment groups (2.34 and 2.33 ± 0.24 for CON vs. FM, respectively; $P = 0.97$), and the model did not reveal any significant interactions between treatment and other factors.

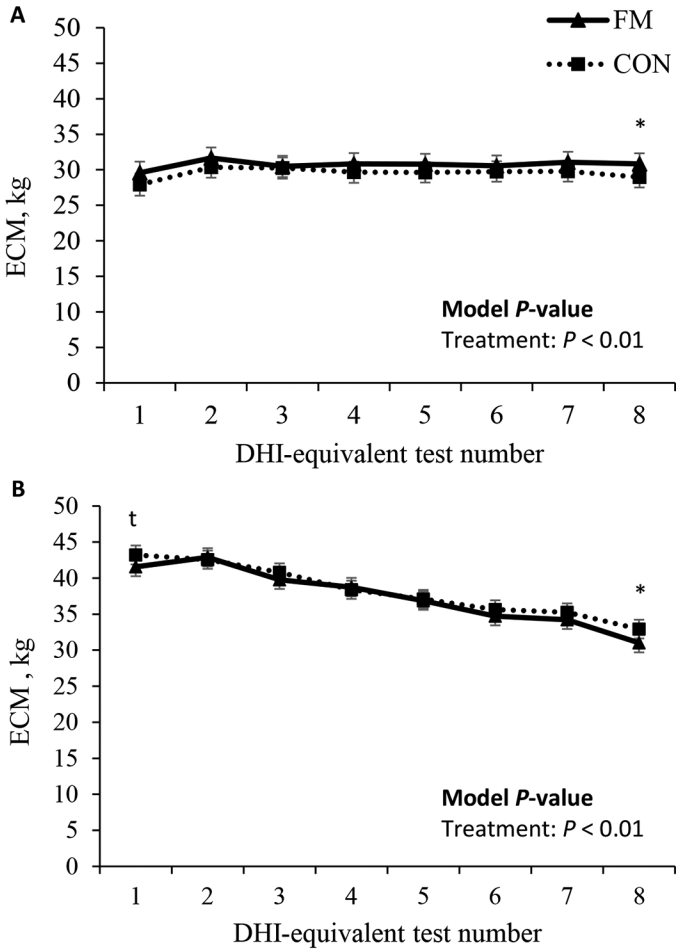

Figure 1. Energy-corrected milk yield over 8 monthly DHI-equivalent tests after calving from (A) primiparous (PRIM) and (B) multiparous (MULT) cows treated with either placebo (CON, n = 78 PRIM, n = 172 MULT) or flunixin meglumine (FM, n = 75 PRIM, n = 175 MULT). t = tendency for a difference ($P < 0.10$); * = significant difference between treatment groups ($P < 0.05$). Error bars represent SEM.

Culling Risk

A total of 14 CON cows and 20 FM cows were either culled or died within the first 60 DIM. Statistically, culling risk within 60 DIM did not differ between treatment groups (hazard ratio for FM vs. CON: 1.20, 95% CI: 0.855–1.693, $P = 0.29$; Figure 2).

Reproductive Performance

No difference in FSCR was observed between treatment groups ($P = 0.82$, odds ratio for FM vs. CON to conceive at first insemination: 0.70, 95% CI: 0.34–1.44). Treatment had no effect on hazard to pregnancy in the first 200 DIM ($P = 0.57$; hazard ratio for FM vs. CON to be diagnosed pregnant by 200 DIM: 1.07, 95%

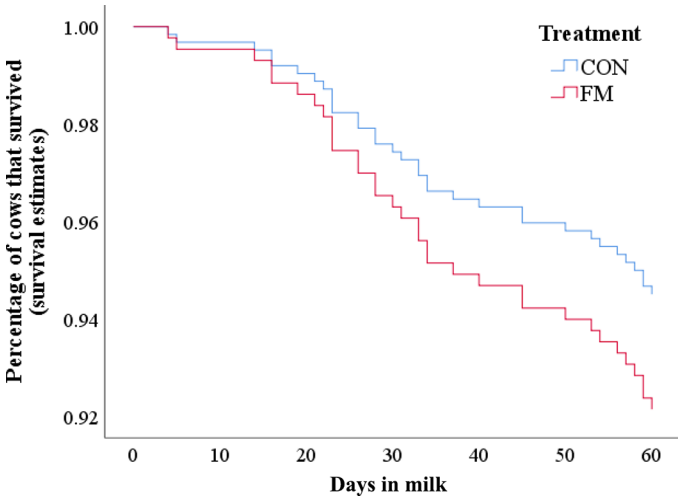

Figure 2. Survival curve derived from a Cox proportional hazard regression model assessing the proportion of cows within treatment: transdermal flunixin meglumine (FM; n = 75 primipara, n = 175 multipara) or placebo (CON; n = 78 primipara, n = 175 multipara) that survived the first 60 DIM. The hazard ratio for FM versus CON was 1.20 (95% CI: 0.855–1.693; $P = 0.29$). Parity was included in the model as fixed effect ($P = 0.22$), and farm was defined as random effect (shared frailty model).

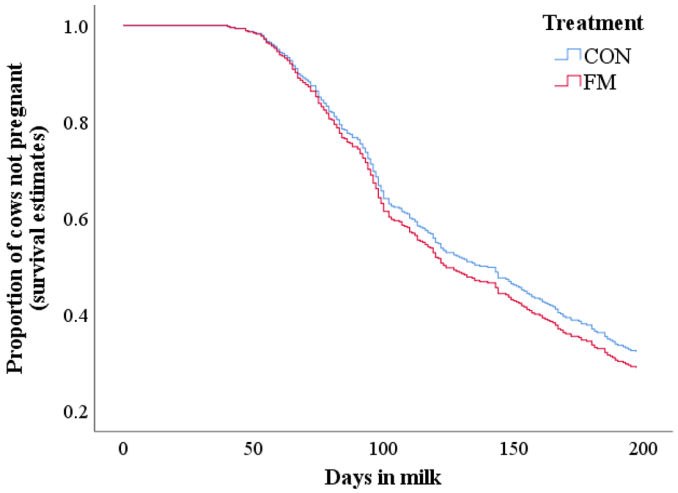

Figure 3. Survival curve derived from a Cox proportional hazard regression model assessing the proportion of cows within treatment: transdermal flunixin meglumine (FM; n = 75 primipara, n = 175 multipara) or placebo (CON; n = 78 primipara, n = 175 multipara) that conceived within 200 DIM. The hazard ratio for FM versus CON was 0.91 (95% CI: 0.727–1.146; $P = 0.43$). Median time to diagnosed pregnancy was 147.0 (95% CI: 126.2–167.8) d for CON and 120.0 (95% CI: 105.0–135.0) d for FM cows. Parity was included in the model as fixed effect ($P = 0.52$), and farm was defined as random effect (shared frailty model).

CI: 0.85–1.34; Figure 3). Median time to diagnosed pregnancy was 147.0 (95% CI: 126.2–167.8) d for CON and 120.0 (95% CI: 105.0–135.0) d for FM cows, respectively. No interaction between parity and treatment was observed. Time to first insemination was included as a covariate ($P < 0.01$).

DISCUSSION

This is the first study to assess the effects of transdermal FM used once in dairy cows 24 to 36 h after calving on production and fertility in subsequent lactation. We hypothesized that FM treatment would alleviate pain and reduce systemic inflammation, thus resulting in higher MY, lower culling risk, and enhanced fertility. In the companion article (Schmitt et al., 2023), we reported the effects of treatment on the cows' laboratory inflammatory and metabolic profile, uterine health, and indicators of pain. Therein, FM-treated PRIM cows showed a slightly lower RT, lower serum concentrations of the acute-phase protein HP, higher serum albumin concentrations, and a lower risk for purulent vaginal discharge with or without a fever compared with PRIM CON cows. In FM-treated MULT cows, however, no treatment effects were found, except for slightly lower serum BHB concentrations. In the present article, we corroborate the abovementioned discrepancies in treatment effects between parities. Statistically, ECM yield from 8 monthly DHI-equivalent tests was significantly greater in PRIM cows treated with FM compared with PRIM CON cows, whereas it was lower in FM-treated MULT cows compared with CON cows. Further, both milk fat and protein yields were greater in FM-treated PRIM cows and lower in FM-treated MULT cows compared with CON cows. No differences in milk urea concentration or LS were observed between treatment groups, and neither culling risk nor fertility (FSCR, DO) was affected by FM treatment.

The present study is the first to report opposing effects of postpartum FM treatment on health and production of PRIM versus MULT cows. Our results partly contradict those of some previous studies assessing the effects of injectable FM around parturition in dairy cows, as these researchers reported either no effect or undesirable treatment effects on inflammatory and metabolic markers (Shwartz et al., 2009; Giammarco et al., 2016) and MY (Shwartz et al., 2009; Giammarco et al., 2016; Newby et al., 2017). Further, 2 studies found higher incidences of RFM in FM-treated cows compared with CON (Waelchli et al., 1999; Newby et al., 2017), which was associated with a higher risk for metritis and lower MY in Newby et al. (2017). Both studies included PRIM and MULT cows but neither reported differences in treatment effects between parities. It should be noted, however, that Waelchli et al. (1999) treated cows directly after relocation of the closed uterus into the abdominal cavity during a ce-

sarean section, and Newby et al. (2017) injected FM within 1 h after calving and again 24 h later in cows with and without dystocia, including the degree of dystocia within their statistical models. By contrast, in our study, treatment was performed within 24 to 36 h after calving in cows that had experienced eutocia with a vital singleton, no signs of MF or RFM, and no high fever, aiming at reducing the risk of provoking RFM by inhibiting prostaglandin synthesis. This may explain the positive effects on postpartum inflammation, uterine health, and MY reported in the present study and our companion article (Schmitt et al., 2023), although these were observed only in PRIM cows. Shwartz et al. (2009) treated cows within 5 h after parturition and daily for the first 3 DIM. In their study, FM treatment reduced both DMI and MY, and increased RT within the first 7 DIM compared with CON. However, overall DMI and ECM within the first 35 DIM were not different among treatment groups. Importantly, only MULT cows were enrolled in the latter study; therefore, the results seem to be similar to our study, as FM-treated MULT cows produced less ECM compared with CON cows. Giammarco et al. (2016), who treated early postpartum cows with either FM, carprofen, or saline (as CON), contradicted the aforementioned studies, reporting an even lower risk of RFM in FM-treated cows compared with CON and carprofen-treated cows. In addition, they found favorable treatment effects of both NSAIDs on culling risk and FSCR. Milk yield and milk components were not affected by treatment. Giammarco et al. (2016) specifically included nonfebrile cows within 12 h after parturition in their study, which might be more similar to our study protocol than those of the aforementioned researchers. Both PRIM and MULT cows were included in their study but effects of parity and interactions between parity and treatment were not reported. However, their sample size was much smaller (n = 20 cows per treatment group), MY was documented until 60 DIM only, and culling risk was observed until 150 DIM, which could explain differences compared with our study.

Flunixin meglumine mainly inhibits the cyclooxygenase enzymes (COX) 1 and 2 (Miciletta et al., 2014) and is a potent antipyretic, anti-inflammatory, and antianalgesic drug (Fraccaro et al., 2013), which might explain the enhanced health, higher feed intake, and increased ECM yields in PRIM cows in our study. However, it is not clear why this was not observed in MULT cows. One possible explanation might be the NSAID-induced reduction of physiological $PGF_{2\alpha}$ in the uterus, impairing physiological processes of uterine involution (Sheldon et al., 2019). The latter could be more crucial in MULT cows because of an additionally higher susceptibility to metabolic disturbances (e.g., subclinical hypocalcemia; Venjakob et al., 2017) and an exacerbated negative energy balance (Xu et al., 2018) compared with PRIM cows. Primiparous cows, on the other hand, are more susceptible to excessive postpartum inflammation (Schneider et al., 2013; Mainau et al., 2014; Pohl et al., 2015); therefore, the effects of NSAID treatment might have been more pronounced here. Further, our inclusion criteria (eutocia with a vital singleton, no signs of MF or RFM, no high fever) and timeframe of administration might have removed all heifers at risk for delayed fetal membrane expulsion and impaired uterine involution from the study population, thereby creating a subsample of PRIM cows that might have benefited from the pharmacological intervention limiting inflammation. However, the positive treatment effect on MY for PRIM cows in the present study was comparably small (+1.19 ± 1.35 kg of ECM for FM-treated PRIM cows compared with CON), which might be due to the single transdermal administration of FM with a relatively short plasma half-life (4–6 h; Kleinhenz et al., 2016).

Some previous studies using different NSAIDs during the periparturient period have observed similar discrepancies in effect size or even contradictory effects between parities. Farney et al. (2013b) reported a 21% increase in whole-lactation MY in third-parity ASA-treated cows compared with CON cows, whereas the MY of PRIM cows treated with ASA tended statistically to be decreased by 8%. Barragan et al. (2020b) found an increase in mature-equivalent MY by 4% in MULT ASA-treated cows (2 oral drenches) compared with CON, whereas no difference between treatment groups was observed in PRIM cows. However, using a more intense treatment protocol (4 oral drenches), Barragan et al. (2020a) observed an increased MY and better reproductive performance (DO) in ASA-treated cows regardless of parity. Recently, the ability of ASA to enhance fertility was confirmed, and a lower risk for clinical metritis in treated cows compared with CON was reported (Barragan et al., 2021). Bertoni et al. (2004) and Carpenter et al. (2016) only included MULT cows in their studies and reported increases in MY of 12% (peak yield) and 8% (305-d mature-equivalent MY). Although Carpenter et al. (2016), who treated cows with oral ASA drenches for 3 d after calving, failed to observe effects on fertility, Bertoni et al. (2004), who injected ASA on 5 consecutive days postpartum, reported better reproductive performance (e.g., FSCR, DO) in treated cows compared with CON cows. The latter study additionally reported a more pronounced BCS loss, lower serum glucose, and higher concentrations of nonesterified fatty acids in the treatment group compared with CON cows, which they attributed to the higher MY. The ability of ASA to alter

glucose metabolism and energy balance, however, has recently been assessed by other researchers and seems to be associated with an enhanced insulin sensitivity of peripheral tissues (Farney et al., 2013a; Montgomery et al., 2019) and altered rumen fermentation (Carpenter et al., 2017). Because the resumption of ovarian activity in early lactation is closely associated with energy metabolism (Castro et al., 2012; Jeong et al., 2015), it is not surprising that a prolonged postpartum treatment protocol with ASA may have stronger effects on fertility compared with either a shorter ASA treatment or the single transdermal administration of FM performed in the present study. Given the longer plasma half-life of FM (4–6 h) compared with ASA (approximately 0.5 h) in cattle, significant effects on fertility and culling risk might have been observed in the present study population with only 2 consecutive treatments, similar to multiple dosages of ASA.

Meloxicam treatment increased MY regardless of parity, but only in those studies that observed MY for a longer period after calving (i.e., at least 7 wk; Carpenter et al., 2016; Shock et al., 2018; Swartz et al., 2018). Swartz et al. (2018) observed even higher daily MY in cows treated with meloxicam before parturition compared with cows treated with meloxicam immediately after parturition and CON cows. Other studies failed to observe meloxicam treatment effects on MY (Newby et al., 2013a; Mainau et al., 2014; Pascottini et al., 2020). Pascottini et al. (2020) treated cows later after calving; that is, within 10 to 13 DIM, and documented daily MY up to 35 DIM only. Newby et al. (2013a) and Mainau et al. (2014) exclusively enrolled cows with assisted calving and cows with eutocia, respectively; treatment was performed within 24 h after parturition in both studies and MY was only documented up to 14 and 30 DIM, respectively.

Ketoprofen was less effective regarding both MY (Richards et al., 2009; Kovacevic et al., 2018) and fertility (Richards et al., 2009), which might be primarily attributable to a lower plasma half-life and different pharmacokinetics of ketoprofen compared with most other NSAIDs (Igarza et al., 2004; Plessers et al., 2015). In fact, 2 injections of ketoprofen immediately and again 24 h after abomasal surgery failed to improve health and production of cows in another study (Newby et al., 2013b), and biomarkers of stress were not altered in cows and calves treated once with ketoprofen after parturition (Gladden et al., 2018).

Differences between studies in general are most likely attributable to different study populations (i.e., geographic location, sample size, lactation numbers), treatment and sampling strategies (i.e., timing and dosing regimen, pharmaceutical agent, administration route, sampling protocol, and methods for sample analysis), outcome variables (e.g., neutrophil activity, time to first insemination, daily MY, monthly MY, ECM), and availability of follow-up data. In comparing studies, it seems that MY must be documented for a longer period after calving to observe treatment effects. It is likely that the use of NSAIDs in the early postpartum period enhances animal health and comfort, which can lead to greater peak yields or cumulated yields (e.g., 305-d MY) but not necessarily to improved MY in early lactation. Early lactation milk production was defined as that in the first 7 to 35 DIM in some of the abovementioned studies (Shwartz et al., 2009; Newby et al., 2013a; Mainau et al., 2014; Pascottini et al., 2020), but it was never affected by NSAID treatment. This might be because early lactation MY is strongly influenced by other factors, such as dry cow ration and management (Lean et al., 2013; Roche et al., 2013).

In general, the abovementioned differences between studies complicate the question of whether to recommend the use of NSAIDs as supportive therapy in both clinically diseased and healthy cows after parturition. The beneficial effects on health, inflammation, and MY of FM in PRIM cows observed in this study might have been more pronounced because farms were selected based on elevated concentrations of HP in a sample of fresh cows (Schmitt et al., 2021). Therefore, whether the treatment of fresh cows with NSAIDs is necessary and economically reasonable may remain a farm-specific decision. Further, overconditioned individuals, cows with subclinical metabolic disorders, and cows experiencing dystocia, twin birth, or stillbirth may benefit even more from such an intervention. Hence, whether NSAID treatment can be specifically targeted to animals at risk should be further investigated [e.g., by determining suitable markers of inflammation in blood (Schmitt et al., 2021) or by using sensors tracking rumination, eating patterns, and activity of transition cows (van Dixhoorn et al., 2018)]. Nonetheless, thorough transition management will always be of utmost importance to ensure a successful start of lactation. The primary goal in transition cow management is, on the one hand, to reduce both metabolic and social stress at calving, and, on the other hand, to enhance cows' resilience toward stressors. This includes optimized body condition, controlled diet, and a hygienic and comfortable environment for calving (Roche et al., 2013). In fact, excessive periparturient immune activation has recently been proposed as a possible underlying cause of many transition disorders (Horst et al., 2021), and approaches toward its prevention (if possible, in the dry-off period) should be investigated in future research.

CONCLUSIONS

The treatment of early postpartum dairy cows with transdermal flunixin meglumine resulted in a slightly greater ECM yield in PRIM cows and a reduced ECM yield in MULT cows compared with CON cows. Culling risk and reproductive performance (FSCR, DO) were not affected by treatment. In farms with high prevalence of postpartum inflammation, the application of transdermal FM can be considered for PRIM cows within 24 to 36 h after calving, provided that the cows are clinically healthy. According to this study, MULT cows should not be treated with transdermal FM within this timeframe. Based on our results, we cannot reach conclusions regarding the use of transdermal FM in cows with dystocia or clinical transition diseases.

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REFERENCES

Ali, A. K. A., and G. E. Shook. 1980. An optimum transformation for somatic cell concentration in milk. J. Dairy Sci. 63:487–490. https://doi.org/10.3168/jds.S0022-0302(80)82959-6.

Barragan, A. A., S. Bas, E. Hovingh, and L. Byler. 2021. Effects of postpartum acetylsalicylic acid on uterine diseases and reproductive performance in dairy cattle. JDS Commun. 2:67–72. https://doi.org/10.3168/jdsc.2020-0047.

Barragan, A. A., L. Bauman, L. da Costa, J. Velez, J. D. R. Gonzalez, G. M. Schuenemann, B. Menichetti, J. Piñeiro, and S. Bas. 2020a. Administration of acetylsalicylic acid after parturition in lactating dairy cows under certified organic management: Part I. Milk yield, milk components, activity patterns, fertility, and health. J. Dairy Sci. 103:11697–11712. https://doi.org/10.3168/jds.2020-18388.

Barragan, A. A., E. Hovingh, S. Bas, J. Lakritz, L. Byler, A. Ludwikowski, S. Takitch, J. Zug, and S. Hann. 2020b. Effects of postpartum acetylsalicylic acid on metabolic status, health, and production in lactating dairy cattle. J. Dairy Sci. 103:8443–8542. https://doi.org/10.3168/jds.2019-17966.

Bell, A. W. 1995. Regulation of organic nutrient metabolism during transition from late pregnancy to early lactation. J. Anim. Sci. 73:2804–2819. https://doi.org/10.2527/1995.7392804x.

Bertoni, G., E. Trevisi, X. Han, and M. Bionaz. 2008. Effects of inflammatory conditions on liver activity in puerperium period and consequences for performance in dairy cows. J. Dairy Sci. 91:3300–3310. https://doi.org/10.3168/jds.2008-0995.

Bertoni, G., E. Trevisi, and F. Piccioli-Cappelli. 2004. Effects of acetyl-salicylate used in post-calving of dairy cows. Vet. Res. Commun. 28:217–219. https://doi.org/10.1023/B:VERC.0000045410.86004.03.

Bradford, B. J., and T. H. Swartz. 2020. Review: Following the smoke signals: Inflammatory signaling in metabolic homeostasis and homeorhesis in dairy cattle. Animal 14(Suppl 1):s144–154. https://doi.org/10.1017/S1751731119003203.

Carpenter, A. J., C. F. V. Rodriguez, J. A. B. Jantz, and B. J. Bradford. 2017. Short communication: Sodium salicylate negatively affects rumen fermentation in vitro and in situ. J. Dairy Sci. 100:1935–1939. https://doi.org/10.3168/jds.2016-11832.

Carpenter, A. J., C. M. Ylioja, C. F. Vargas, L. K. Mamedova, L. G. Mendonca, J. F. Coetzee, L. C. Hollis, R. Gehring, and B. J. Bradford. 2016. Hot topic: Early postpartum treatment of commercial dairy cows with nonsteroidal antiinflammatory drugs increases whole-lactation milk yield. J. Dairy Sci. 99:672–679. https://doi.org/10.3168/jds.2015-10048.

Castro, N., C. Kawashima, H. A. van Dorland, I. Morel, A. Miyamoto, and R. M. Bruckmaier. 2012. Metabolic and energy status during the dry period is crucial for the resumption of ovarian activity postpartum in dairy cows. J. Dairy Sci. 95:5804–5812. https://doi.org/10.3168/jds.2012-5666.

Chebel, R. C., P. R. B. Silva, M. I. Endres, M. A. Ballou, and K. L. Luchterhand. 2016. Social stressors and their effects on immunity and health of periparturient dairy cows. J. Dairy Sci. 99:3217–3228. https://doi.org/10.3168/jds.2015-10369.

Drackley, J. K. 1999. Biology of dairy cows during the transition period: The final frontier? J. Dairy Sci. 82:2259–2273. https://doi.org/10.3168/jds.S0022-0302(99)75474-3.

Farney, J. K., L. K. Mamedova, J. F. Coetzee, B. KuKanich, L. M. Sordillo, S. K. Stoakes, J. E. Minton, L. C. Hollis, and B. J. Bradford. 2013a. Anti-inflammatory salicylate treatment alters the metabolic adaptations to lactation in dairy cattle. Am. J. Physiol. Regul. Integr. Comp. Physiol. 305:R110–R117. https://doi.org/10.1152/ajpregu.00152.2013.

Farney, J. K., L. K. Mamedova, J. F. Coetzee, J. E. Minton, L. C. Hollis, and B. J. Bradford. 2013b. Sodium salicylate treatment in early lactation increases whole-lactation milk and milk fat yield in mature dairy cows. J. Dairy Sci. 96:7709–7718. https://doi.org/10.3168/jds.2013-7088.

Fraccaro, E., J. F. Coetzee, R. Odore, L. N. Edwards-Callaway, B. KuKanich, P. Badino, L. Bertolotti, H. Glynn, J. Dockweiler, K. Allen, and L. Bergamasco. 2013. A study to compare circulating flunixin, meloxicam and gabapentin concentrations with prostaglandin E(2) levels in calves undergoing dehorning. Res. Vet. Sci. 95:204–211. https://doi.org/10.1016/j.rvsc.2013.01.018.

Giammarco, M., I. Fusaro, G. Vignola, A. Manetta, A. Gramenzi, M. Fustini, A. Palmonari, and A. Formigoni. 2016. Effects of a single injection of Flunixin meglumine or Carprofen postpartum on haematological parameters, productive performance and fertility of dairy cattle. Anim. Prod. Sci. 58:322. https://doi.org/10.1071/AN16028.

Gladden, N., D. McKeegan, L. Viora, and K. A. Ellis. 2018. Postpartum ketoprofen treatment does not alter stress biomarkers in cows and calves experiencing assisted and unassisted parturition: A randomised controlled trial. Vet. Rec. 183:414. https://doi.org/10.1136/vr.104913.

Goff, J. P., and R. L. Horst. 1997. Physiological changes at parturition and their relationship to metabolic disorders. J. Dairy Sci. 80:1260–1268. https://doi.org/10.3168/jds.S0022-0302(97)76055-7.

Horst, E. A., S. K. Kvidera, and L. H. Baumgard. 2021. Invited review: The influence of immune activation on transition cow health and performance—A critical evaluation of traditional dogmas. J. Dairy Sci. 104:8380–8410. https://doi.org/10.3168/jds.2021-20330.

Horst, R. L., J. P. Goff, and T. A. Reinhardt. 2005. Adapting to the transition between gestation and lactation: Differences between rat, human and dairy cow. J. Mammary Gland Biol. Neoplasia 10:141–156. https://doi.org/10.1007/s10911-005-5397-x.

Igarza, L., A. Soraci, N. Auza, and H. Zeballos. 2004. Some pharmacokinetic parameters of R-(−)- and S-(+)ketoprofen: The influence of age and differing physiological status in dairy cattle. Vet. Res.

Commun. 28:81–87. https://doi.org/10.1023/B:VERC.0000009534.64533.b9.
Jeong, J. K., I. S. Choi, H. G. Kang, T. Y. Hur, Y. H. Jung, and I. H. Kim. 2015. Relationship between serum metabolites, body condition, peri- and postpartum health and resumption of postpartum cyclicity in dairy cows. Livest. Sci. 181:31–37. https://doi.org/10.1016/j.livsci.2015.09.022.
Kelton, D. F., K. D. Lissemore, and R. E. Martin. 1998. Recommendations for recording and calculating the incidence of selected clinical diseases of dairy cattle. J. Dairy Sci. 81:2502–2509. https://doi.org/10.3168/jds.S0022-0302(98)70142-0.
Kleinhenz, M. D., N. K. van Engen, P. J. Gorden, B. KuKanich, S. M. Rajewski, P. Walsh, and J. F. Coetzee. 2016. The pharmacokinetics of transdermal flunixin meglumine in Holstein calves. J. Vet. Pharmacol. Ther. 39:612–615. https://doi.org/10.1111/jvp.12314.
Kovacevic, Z., D. Stojanovic, M. Cincovic, B. Belic, I. Davidov, N. Plavsa, and M. Radinovic. 2018. Association of metabolic and inflammatory markers with milk yield in postpartum dairy cows treated with ketoprofen. Pol. J. Vet. Sci. 21:325–331. https://doi.org/10.24425/122600.
Lean, I. J., R. van Saun, and P. J. Degaris. 2013. Mineral and antioxidant management of transition dairy cows. Vet. Clin. North Am. Food Anim. Pract. 29:367–386. https://doi.org/10.1016/j.cvfa.2013.03.004.
Mainau, E., A. Cuevas, J. L. Ruiz-de-la-Torre, E. Abbeloos, and X. Manteca. 2014. Effect of meloxicam administration after calving on milk production, acute phase proteins, and behavior in dairy cows. J. Vet. Behav. 9:357–363. https://doi.org/10.1016/j.jveb.2014.07.007.
McArt, J. A. A., D. V. Nydam, and G. R. Oetzel. 2012. Epidemiology of subclinical ketosis in early lactation dairy cattle. J. Dairy Sci. 95:5056–5066. https://doi.org/10.3168/jds.2012-5443.
Meier, S., N. V. Priest, C. R. Burke, J. K. Kay, S. McDougall, M. D. Mitchell, C. G. Walker, A. Heiser, J. J. Loor, and J. R. Roche. 2014. Treatment with a nonsteroidal antiinflammatory drug after calving did not improve milk production, health, or reproduction parameters in pasture-grazed dairy cows. J. Dairy Sci. 97:2932–2943. https://doi.org/10.3168/jds.2013-7838.
Miciletta, M., B. Cuniberti, R. Barbero, and G. Re. 2014. In vitro enantioselective pharmacodynamics of Carprofen and Flunixin-meglumine in feedlot cattle. J. Vet. Pharmacol. Ther. 37:43–52. https://doi.org/10.1111/jvp.12052.
Montgomery, S. R., L. K. Mamedova, M. Zachut, G. Kra, S. Haussler, M. Vaughn, J. Gonzalez, and B. J. Bradford. 2019. Effects of sodium salicylate on glucose kinetics and insulin signaling in postpartum dairy cows. J. Dairy Sci. 102:1617–1629. https://doi.org/10.3168/jds.2018-15312.
Nagel, C., L. Trenk, C. Aurich, N. Ille, M. Pichler, M. Drillich, W. Pohl, and J. Aurich. 2016. Sympathoadrenal balance and physiological stress response in cattle at spontaneous and PGF2alpha-induced calving. Theriogenology 85:979–985. https://doi.org/10.1016/j.theriogenology.2015.11.009.
Newby, N. C., K. E. Leslie, H. D. P. Dingwell, D. F. Kelton, D. M. Weary, L. Neuder, S. T. Millman, and T. F. Duffield. 2017. The effects of periparturient administration of flunixin meglumine on the health and production of dairy cattle. J. Dairy Sci. 100:582–587. https://doi.org/10.3168/jds.2016-11747.
Newby, N. C., D. L. Pearl, S. J. Leblanc, K. E. Leslie, M. A. von Keyserlingk, and T. F. Duffield. 2013a. Effects of meloxicam on milk production, behavior, and feed intake in dairy cows following assisted calving. J. Dairy Sci. 96:3682–3688. https://doi.org/10.3168/jds.2012-6214.
Newby, N. C., D. L. Pearl, S. J. LeBlanc, K. E. Leslie, M. A. von Keyserlingk, and T. F. Duffield. 2013b. The effect of administering ketoprofen on the physiology and behavior of dairy cows following surgery to correct a left displaced abomasum. J. Dairy Sci. 96:1511–1520. https://doi.org/10.3168/jds.2012-5566.
Pascottini, O. B., S. J. van Schyndel, J. F. W. Spricigo, M. R. Carvalho, B. Mion, E. S. Ribeiro, and S. J. Leblanc. 2020. Effect of anti-inflammatory treatment on systemic inflammation, immune function, and endometrial health in postpartum dairy cows. Sci. Rep. 10:5236. https://doi.org/10.1038/s41598-020-62103-x.
Plessers, E., A. Watteyn, H. Wyns, B. Pardon, S. de Baere, P. de Backer, and S. Croubels. 2015. Enantioselective pharmacokinetics of ketoprofen in calves after intramuscular administration of a racemic mixture. J. Vet. Pharmacol. Ther. 38:410–413. https://doi.org/10.1111/jvp.12186.
Pohl, A., O. Burfeind, and W. Heuwieser. 2015. The associations between postpartum serum haptoglobin concentration and metabolic status, calving difficulties, retained fetal membranes, and metritis. J. Dairy Sci. 98:4544–4551. https://doi.org/10.3168/jds.2014-9181.
Reinhardt, T. A., J. D. Lippolis, B. J. McCluskey, J. P. Goff, and R. L. Horst. 2011. Prevalence of subclinical hypocalcemia in dairy herds. Vet. J. 188:122–124. https://doi.org/10.1016/j.tvjl.2010.03.025.
Richards, B. D., D. H. Black, R. M. Christley, M. D. Royal, R. F. Smith, and H. Dobson. 2009. Effects of the administration of ketoprofen at parturition on the milk yield and fertility of Holstein-Friesian cattle. Vet. Rec. 165:102–106. https://doi.org/10.1136/vetrec.165.4.102.
Roche, J. R., A. W. Bell, T. R. Overton, and J. J. Loor. 2013. Nutritional management of the transition cow in the 21st century—A paradigm shift in thinking. Anim. Prod. Sci. 53:1000. https://doi.org/10.1071/AN12293.
Rodríguez, E. M., A. Aris, and A. Bach. 2017. Associations between subclinical hypocalcemia and postparturient diseases in dairy cows. J. Dairy Sci. 100:7427–7434. https://doi.org/10.3168/jds.2016-12210.
Schmitt, R., L. Pieper, S. Borchardt, J. M. Swinkels, C.-C. Gelfert, and R. Staufenbiel. 2023. Effects of a single transdermal administration of flunixin meglumine in early postpartum Holstein Friesian dairy cows: Part 1. Inflammatory and metabolic markers, uterine health, and indicators of pain. J. Dairy Sci. 106:624–640. https://doi.org/10.3168/jds.2021-20555.
Schmitt, R., L. Pieper, L. A. Gonzalez-Grajales, J. Swinkels, C.-C. Gelfert, and R. Staufenbiel. 2021. Evaluation of different acute-phase proteins for herd health diagnostics in early postpartum Holstein Friesian dairy cows. J. Dairy Res. 88:33–37. https://doi.org/10.1017/S0022029921000078.
Schneider, A., M. N. Correa, and W. R. Butler. 2013. Short communication: acute phase proteins in Holstein cows diagnosed with uterine infection. Res. Vet. Sci. 95:269–271. https://doi.org/10.1016/j.rvsc.2013.02.010.
Schuenemann, G. M., I. Nieto, S. Bas, K. N. Galvão, and J. Workman. 2011. Assessment of calving progress and reference times for obstetric intervention during dystocia in Holstein dairy cows. J. Dairy Sci. 94:5494–5501. https://doi.org/10.3168/jds.2011-4436.
Sheldon, I. M., J. G. Cronin, and J. J. Bromfield. 2019. Tolerance and innate immunity shape the development of postpartum uterine disease and the impact of endometritis in dairy cattle. Annu. Rev. Anim. Biosci. 7:361–384. https://doi.org/10.1146/annurev-animal-020518-115227.
Sheldon, I. M., D. E. Noakes, A. N. Rycroft, D. U. Pfeiffer, and H. Dobson. 2002. Influence of uterine bacterial contamination after parturition on ovarian dominant follicle selection and follicle growth and function in cattle. Reproduction 123:837–845. https://doi.org/10.1530/rep.0.1230837.
Shock, D. A., D. L. Renaud, S. M. Roche, R. Poliquin, R. Thomson, and M. E. Olson. 2018. Evaluating the impact of meloxicam oral suspension administered at parturition on subsequent production, health, and culling in dairy cows: A randomized clinical field trial. PLoS One 13:e0209236. https://doi.org/10.1371/journal.pone.0209236.
Shwartz, G., K. L. Hill, M. J. VanBaale, and L. H. Baumgard. 2009. Effects of flunixin meglumine on pyrexia and bioenergetic variables in postparturient dairy cows. J. Dairy Sci. 92:1963–1970. https://doi.org/10.3168/jds.2008-1581.
Sordillo, L. M., G. A. Contreras, and S. L. Aitken. 2009. Metabolic factors affecting the inflammatory response of periparturient dairy cows. Anim. Health Res. Rev. 10:53–63. https://doi.org/10.1017/S1466252309990016.

Spiekers, H., and V. Potthast. 2009. Erläuterung von Begriffen der Futterkonservierung und Tierernährung. Pages 12–13 in Erfolgreiche Milchviehfütterung. 5th ed. DLG-Verlag.

Stilwell, G., H. Schubert, and D. M. Broom. 2014. Short communication: Effects of analgesic use postcalving on cow welfare and production. J. Dairy Sci. 97:888–891. https://doi.org/10.3168/jds.2013-7100.

Swartz, T. H., H. H. Schramm, J. M. Bewley, C. M. Wood, K. E. Leslie, and C. S. Petersson-Wolfe. 2018. Meloxicam administration either prior to or after parturition: Effects on behavior, health, and production in dairy cows. J. Dairy Sci. 101:10151–10167. https://doi.org/10.3168/jds.2018-14657.

van Dixhoorn, I. D. E., R. M. de Mol, J. T. N. van der Werf, S. van Mourik, and C. G. van Reenen. 2018. Indicators of resilience during the transition period in dairy cows: A case study. J. Dairy Sci. 101:10271–10282. https://doi.org/10.3168/jds.2018-14779.

Vannucchi, C. I., J. A. Rodrigues, L. C. Silva, C. F. Lucio, G. A. Veiga, P. V. Furtado, C. A. Oliveira, and M. Nichi. 2015. Association between birth conditions and glucose and cortisol profiles of periparturient dairy cows and neonatal calves. Vet. Rec. 176:358. https://doi.org/10.1136/vr.102862.

Venjakob, P. L., S. Borchardt, and W. Heuwieser. 2017. Hypocalcemia—Cow-level prevalence and preventive strategies in German dairy herds. J. Dairy Sci. 100:9258–9266. https://doi.org/10.3168/jds.2016-12494.

Vieira-Neto, A., F. S. Lima, J. E. P. Santos, R. D. Mingoti, G. S. Vasconcellos, C. A. Risco, and K. N. Galvao. 2016. Vulvovaginal laceration as a risk factor for uterine disease in postpartum dairy cows. J. Dairy Sci. 99:4629–4637. https://doi.org/10.3168/jds.2016-10872.

Waelchli, R. O., R. Thun, and H. Stocker. 1999. Effect of flunixin meglumine on placental expulsion in dairy cattle after a cesarean. Vet. Rec. 144:702–703. https://doi.org/10.1136/vr.144.25.702.

Xu, W., J. Vervoort, E. Saccenti, R. van Hoeij, B. Kemp, and A. van Knegsel. 2018. Milk metabolomics data reveal the energy balance of individual dairy cows in early lactation. Sci. Rep. 8:15828. https://doi.org/10.1038/s41598-018-34190-4.

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