J. Dairy Sci. TBC
https://doi.org/10.3168/jds.2024-24885

Effects of calving interval of dairy cows on development, metabolism and milk performance of their offspring

Yapin Wang,[1]* Allyson Ipema,[1] Roselinde Goselink,[2] Eline Burgers,[1,2] Josef Gross,[3] Rupert Bruckmaier,[3] Bas Kemp,[1] and Ariette van Knegsel[1]
[1]Adaptation Physiology Group, Wageningen University & Research, PO Box 338, 6700 AH Wageningen, the Netherlands
[2]Wageningen Livestock Research, Wageningen University & Research, PO Box 338, 6700 AH Wageningen, the Netherlands
[3]Veterinary Physiology, Vetsuisse Faculty, University of Bern, Bremgartenstrasse 109a, CH-3001 Bern, Switzerland

ABSTRACT

Extending the voluntary waiting period (**VWP**) for insemination in dairy cows is of interest to reduce the frequency of calving events and inseminate at a moment with fewer fertility problems. Little is known about the calves born from dams with a different VWP followed by a different calving interval (**CInt**). The objective of the current study was to identify the effect of dam's CInt on body condition, metabolic status, and milk production of their offspring from birth till 100 DIM of the offspring's first lactation. Holstein Friesian dairy cows (n = 154, 41 primiparous, 113 multiparous) were blocked according to parity, milk yield, and somatic cell count (**SCC**), and randomly assigned to a VWP of 50, 125, or 200 d. Female calves (n = 62) from cows with different CInt were monitored from birth until their first calving event as heifer. Certain dams were not successfully inseminated soon after the planned VWP, resulting in differences between the intended VWP and the actual CInt. Calves were regrouped according to their dam's actual CInt (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d). The dam's CInt did not affect calf birth weight. From birth to weaning, the calves born to dams in CInt_1 (0.34 mmol/L (confidence interval (**CI**): 0.30, 0.37) had a higher plasma nonesterified fatty acids (**NEFA**) concentration than CInt_2 (0.28 mmol/L (CI: 0.26, 0.31)) and CInt_3 (0.26 mmol/L (CI: 0.24, 0.29)) calves. Calves born to dams with a shorter CInt (CInt_1) had greater IgG and IgM against keyhole limpet hemocyanin (**KLH**) than CInt_3 (IgG: 6.05 ± 0.30 vs. 4.64 ± 0.30; IgM: 6.45 ± 0.17 vs. 5.89 ± 0.16, respectively) before weaning. After weaning till calving, CInt_1-calves tended to have greater plasma NEFA concentration than CInt_3-calves. During the first 100 d in milk, a longer CInt of the dams resulted in lower plasma IGF_1 (CInt_2), lower milk lactose (CInt_3) and fat and protein corrected milk (**FPCM**) (CInt_2) in offspring, compared with shorter CInt of the dams (CInt_1). Collectively, a longer CInt in dams did not affect birth weight of their calves or body weight during the weaning or rearing phase. From birth till weaning, a longer CInt in dams resulted in less IgG against KLH and lower plasma NEFA concentration in plasma of the calves. During the first lactation of their offspring, a longer CInt in dams can result in a lower plasma IGF_1 and FPCM during the first 100 DIM, although effects were not present in all CInt categories.
Key words: extended calving interval, maternal effect, fetal programming, calf, heifer

INTRODUCTION

In humans, it is known that nutritional status and metabolism of mothers during pregnancy is related to growth, development, and health of the infant during the prenatal and postnatal period and even during adult life. This phenomenon is known as 'fetal programming', as reviewed by Lee (2015). Also in animals, maternal nutrient and metabolic status affected fetal development and had long-term consequences for their offspring (Carvalho et al., 2020, Wallace et al., 2020, Carcea et al., 2021). For instance, studies in sheep reported that lamb's body weight at weaning and average daily gain from birth to weaning tended to increase linearly as maternal metabolizable protein intake increased during late gestation from 60% of metabolizable protein requirements to 80% and even up to 100% (van Emon et al., 2014). In addition, pups from rats fed high-fat diet for the 3 wk before mating and throughout pregnancy and lactation had upregulated inflammatory response as adults (Latouche et al., 2014). However, these effects may be attributed to the maternal diet during pregnancy, the dams' diet during early life of the pups, or a combination of both.

In dairy cows, a limited number of studies have evaluated the maternal effects during pregnancy on develop-

Received March 8, 2024.
Accepted May 27, 2024.
*Corresponding author: Yapin Wang, yapin.wang@wur.nl

The list of standard abbreviations for JDS is available at adsa.org/jds-abbreviations-24. Nonstandard abbreviations are available in the Notes.

ment, immunity and metabolic status of the calf after birth (Berry et al., 2008, Bossaert et al., 2014, Kamal et al., 2014). Maternal supplementation with folic acid and cobalt combined with rumen-protected methionine reduced inflammatory status in calves as indicated by lower plasma haptoglobin at birth and increased mRNA abundance of intercellular adhesion molecule during the neonatal period (Lopes et al., 2021). Another study reported that blood glucose, IGF-1 and nonesterified fatty acids (**NEFA**) concentrations in cows during early gestation were not related with birth weight, blood glucose and insulin of calves between 7 and 14 d of age (Bossaert et al., 2014). Not only during the prenatal period, but also during the first few hours of life the cow can affect health and development of her calf, which happens via colostrum. Calves do not receive maternal antibodies during the fetal period, due to the placental barrier in cattle (Baintner, 2007), and plasma antibody concentrations are high after colostrum intake (Donovan et al., 2007).

Extending the voluntary waiting period for insemination (**VWP**) gives cows more time to recover from calving and start of lactation (Gaillard et al., 2019, van Knegsel et al., 2022). Some dairy farmers deliberately extend the interval from calving to first insemination to reduce the number and frequency of critical calving events for the cow (Burgers et al., 2021). Extending VWP affects fertility (Niozas et al., 2019, Ma et al., 2022a), milk production (Österman and Bertilsson, 2003, Burgers et al., 2021), and body condition (Jarman et al., 2020) of dams during different periods of the lactation (Burgers et al., 2021). In detail, during 8 wk around the end of the VWP, multiparous cows with an extended VWP length of 200 d (**VWP200**) had higher plasma IGF-1 concentration, and lower fat and protein corrected milk yield (**FPCM**) than cows with an extended VWP length of 50 d (**VWP50**) or 125 d (**VWP125**) (Burgers et al., 2021). During pregnancy, multiparous cows in VWP200 had higher insulin, IGF-1, better body condition score (**BCS**), and lower FPCM than cows in VWP50 or VWP125 (Burgers et al., 2023). It can be hypothesized that as extending the VWP alters the metabolic status, body condition and milk production around conception and during pregnancy, this could also affect the unborn calf. The objective of the current study is to identify the effect of dam's CInt on body condition, metabolic status, and milk production of their offspring from birth till 100 DIM of the offspring's first lactation.

MATERIALS AND METHODS

Animals and Experimental Design

The experimental protocol was approved by the Institutional Animal Care and Use Committee of Wageningen University & Research (the Netherlands) and complied with the Dutch law on Animal Experimentation (approval number: AVD401002016653). The experiment was executed at Dairy Campus research farm (Leeuwarden, the Netherlands). In this experiment, all calves were born to cows that were inseminated after different VWPs. The animals, experimental design and treatments have been described earlier (Burgers et al., 2021, Ma et al., 2022a). In short, Holstein-Friesian dairy cows (n = 154, 41 primiparous, 113 multiparous) were blocked according to parity, milk yield, and somatic cell count (**SCC**), and randomly assigned to one of the 3 VWPs with insemination from d 50, 125, or 200 d post calving onwards. Cows were milked twice daily and housed in free stalls. For the current study, female calves born after the different insemination protocols were monitored (n = 62, 17 from primiparous, 45 from multiparous) from birth to weaning until 100 d in milk. Timing of pregnancy during lactation was determined by 1. The VWP of the dams, and 2. Time to pregnancy after end of the VWP. Therefore, calves were regrouped into 3 groups according to the true calving interval (**CInt**) of their dams (**Table 1)** (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d). The experiment was conducted at 2 locations, including Dairy Campus research farm (Leeuwarden, the Netherlands) for calving and lactation and Dairy Campus young stock farm (Westergeest, the Netherlands) for calf rearing.

Animal Management

Housing. All calves were individually housed after birth in calf igloos on straw, in the open air. In winter, the igloos were moved to the shed. After 7 d of age, they were housed in groups on straw in a calf igloo, with the drinking machine (Förster, Engen, Germany). When they were at least 14 d of age and healthy, they were transported to the young stock farm every 2 wks. At the young stock farm, the calves were housed on straw in 2 age groups: 1. From arrival at the young stock farm till 3 mo of age; and 2. From 3 to 6 mo of age. From the age of 6 mo, the animals came in groups in a loose barn area with cubicles, with rubber cow mattresses. Around last 5–6 weeks before the expected calving date, the animals returned to dairy research farm biweekly, where they were housed in the barn with dry cows and calving cows. After calving, the animals were housed in a cubicle shed and milked twice a day in the 40-stand rotary parlor (GEA, Dusseldorf, Germany). Disease treatments of dams and heifer calves occurred according to Dairy Campus protocol (Burgers et al., 2021).

Feeding and drinking. Drinking water was provided unlimited during the entire trial period. Within the first day after birth, colostrum from the calf's own mother

Table 1. Calving interval of the 62 dairy cows that gave birth to heifer calves, per voluntary waiting period after calving until first insemination of 50, 125, or 200 d (VWP50, VWP125, or VWP200), and per calving interval group (CInt) (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d)

				Number of animals (at birth)	
VWP	Calving interval (d)	SEM[1]	Range	From primiparous	From multiparous
VWP50	385[c]	9.09	324 - 536	7	19
VWP125	456[b]	10.63	405 - 586	7	12
VWP200	507[a]	11.24	469 - 575	3	14
P-value	<0.01				
CInt					
CInt_1	360[c]	6.53	324 - 408	5	14
CInt_2	434[b]	6.36	411 - 459	7	13
CInt_3	512[a]	5.94	469 - 586	5	18
P-value	<0.01				

[a, b] Different superscript letters indicate a difference among LSM within the column ($P < 0.05$).

[1]SEM = standard error of the mean.

was given twice (2 × 2 L) by teat bucket or teat bottle, after which it was switched to milk replacer (Denkamilk Excellent, Denkavit, Voorthuizen, the Netherlands) in accordance with the young stock breeding protocol at the Dairy Campus. On arrival at the young stock farm, calves were fed with the same milk replacer according to the schedule (**Supplementary Table S1**). Milk replacer was given until approximately 11 weeks of age after which they were weaned gradually. In addition, calves were given unlimited Vita Comfort (ForFarmers, Lochem, the Netherlands), which is a mixture of concentrates, chopped short and dedusted wheat straw and molasses, from 2 wks of age to approximately 4–4.5 mo, in which they took in approximately 3.5–4 kg per day. From about 4–4.5 mo of age onwards, unlimited grass silage was provided. Till 6 mo of age, supplementary young stock concentrates were provided (Vitabrok Compleet, ForFarmers, Lochem, the Netherlands).

Insemination. Animals were inseminated from an age of approximately 12–12.5 mo, when they had reached a body weight of at least 370 kg and were in heat on the basis of Nedap Smarttag heat detection (Nedap, Groenlo, the Netherlands). At the end of gestation, the animals returned to dairy research farm with biweekly transport.

Sampling and Measurements

Body condition. Body weight was registered at birth and subsequently every 2 wks till 12 wk of age using the scale for body weight (Welvaarts, 's-Hertogenbosch, the Netherlands). From 12 wk of age until return to the dairy farm, body weight was measured every 2 mo. After calving, body weight was automatically recorded twice daily after milking, by a scale that the cows walked over when returning from the milking rotary to the frees tall. Body condition score was visually evaluated every 4 wks by the same person using a 1 to 5 scale, in which 1 is the leanest score and 5 is the fattest (Ferguson et al., 1994)

Blood sampling and analysis. Blood was taken into evacuated EDTA and heparin tubes (Vacuette, Greiner BioOne, Kremsmunster, Austria) from the jugular vein until the age of about 12 mo, after which the tail vein was used. Blood samples were collected after birth before colostrum intake (d 0), after colostrum intake (d 1), and subsequently taken every 2 wks on a fixed day in the week till 12 wk of age. From 12 wk of age until calving, blood samples were taken every 4 mo on a fixed day in the month. After calving, samples were collected weekly on a fixed day in the week from wk 1 to 8, and subsequently every 2 wks until 16 wk in lactation. Samples were kept on ice before centrifugation (3,000 × g for 15 min, 4°C) for plasma isolation and then stored at −20°C.

Plasma insulin, IGF-1, and growth hormone concentrations were assessed as described earlier (Vicari et al., 2008). Furthermore, plasma metabolite concentrations from EDTA tubes were assessed through an autoanalyzer (Cobas Mira, Roche, Switzerland). This analysis involved the use of enzymatic kits for various metabolites: glucose: GLUC3 08057800190; urea: UREAL 08058806190; β-hydroxybutyric acid (**BHB**): Ranbut RB1007/RB1008; NEFA: and NEFA FA115 (Randox Laboratories Ltd. And Roche Laboratories Ltd. Schwyz, Switzerland). Preliminary analysis showed that BHB in early life of the calves was below the detection limit (<0.100 mmol/L) of the kit, and therefore not presented.

The measurement of natural antibodies against keyhole limpet hemocyanin (**KLH**) in plasma from heparin tubes was conducted using an indirect 2-step ELISA as described by de Koning et al. (2015) and Mayasari et al. (2015). Plates (Greiner Bio-one, Alphen a/d Rijn, the Netherlands) were coated with 2 µg/mL of KLH in 100 µL coating buffer (5.3 g/L Na_2CO_3, 4.2 g/L $NaHCO_3$). Plasma samples were 1:10 prediluted and subsequently

4-step wise diluted in the antigen-coated plates with dilution buffer (phosphate buffered saline (PBS; 10.26 g/L $Na_2HPO_4 \cdot H_2O$, 2.36 g/L KH_2PO_4, 4.5 g/L NaCl; pH 7.2) containing 0.05% Tween 20® and 1% normal horse serum). One unrelated pool of cow plasma served as a standard control. Natural antibodies of IgG isotype in plasma were detected using 1:10,000 dilution of sheep polyclonal anti-bovine IgG-heavy chain conjugated to horseradish peroxidase (**HRP**) (Catalog Number A10–118P, Bethyl Laboratories). Natural antibodies of IgM isotype in plasma were measured using 1:40,000 dilution of rabbit polyclonal anti-bovine IgM-heavy chain conjugated to HRP (Catalog Number A10–100P, Bethyl Laboratories). Antibody titers were calculated as described by de Koning et al. (2015) and Mayasari et al. (2015).

Colostrum and milk sampling. The first colostrum yield after calving was recorded (kg), mixed, sampled in a 10 mL tube without preservative and stored at −20°C. The concentration of IgG and IgM in colostrum was determined with an indirect ELISA method using a bovine IgG ELISA Quantitation Kit and a bovine IgM ELISA Quantitation Kit (Bethyl Laboratories Inc., Montgomery, Texas). The used dilutions were 1:2000,000 for IgG and 1:50,000 for IgM after multiple test dilutions.

Milk yield of those heifers was recorded twice daily automatically and was summed per day. Milk composition of one evening and one morning sample was determined weekly for milk fat, milk protein, milk lactose percentage, SCC, and milk urea concentration (ISO 9622, 2013, Qlip, Zutphen, the Netherlands). The FPCM was calculated as follows (CVB, 2016):

$$\text{FPCM (kg)} = \text{milk yield (kg)} \times (0.337 + 0.116 \times \text{Fat (\%)} + 0.06 \times \text{Protein (\%)})$$

This calculation is based on the weekly fat and protein percentages and the mean daily milk yield for each week.

Statistical Analysis

All statistical analyses were conducted using SAS version 9.4 (SAS Inst. Inc., Cary, NC). To assess normal distribution, the normality test was employed (PROC UNIVARIATE). For data that did not follow a normal distribution, a logarithmic transformation was applied. Back-transformed values are presented in tables and figures. Values are presented as least squares means (**LSM**) ± maximum standard error of the mean (**SEM**) or confidence interval (**CI**) for back-transformed data. All *P*-values of pair-wise comparisons of LSM were corrected with a Tukey's HSD correction for multiple comparisons. Differences were regarded significant if *P*-values <0.05 and as a tendency if $0.05 \leq P$-values <0.10 after Tukey correction for multiple comparisons.

First, data was analyzed separately for 3 different phases of life: from birth to weaning at 11 wk of age, from weaning to calving, and first 100 DIM after their first calving. Second, in preliminary analysis, birth season and sire (n = 23) as random effects were analyzed. However, no significant differences were observed when considering the birth season as a random effect, while sire as a random effect yielded a statistically significant outcome. Consequently, in subsequent analyses, we retained sire as the random effect and omitted birth season from the model. For all plasma variables from birth to weaning, excluding IGF-1, and during the 100DIM of the first lactation, excluding growth hormone and insulin, a heterogeneous first order autoregressive covariance structure was the best fit based on Akaike's corrected information criterion and was used to account for within-cow variation. For all other variables, a homogeneous first order autoregressive covariance structure was the best fit based on Akaike's corrected information criterion and was used to account for within-cow variation.

All data were analyzed using general linear mixed models (PROC MIXED) that included a fixed effect of CInt (CInt_1, CInt_2, or CInt_3), parity class of the dam (primiparous or multiparous) and (in all models except for birth weight, plasma metabolites before and after colostrum intake, colostrum variables, number of inseminations per pregnancy, age at first calving) a factor of time that differed between models (explained below), as well as their 2-way interactions. When a fixed effect of time was included, the model also contained a repeated effect of time with calf or heifer as subject.

Additionally, variable CInt of 62 dams was analyzed, without parity class and time effect in the model.

From birth to weaning. From birth to weaning, plasma IgG against KLH, IgM against KLH, growth hormone, IGF-1, insulin, glucose, urea, and NEFA were analyzed with a time effect included as age in month (d 0, d 1, mo 0.5, 1, 1.5, 2, 2.5). Body weight was analyzed using a time effect of age in month (mo 0, 0.5, 1, 1.5, 2, 2.5). This analysis was conducted for all calves that had samples during this period (n = 61). Before and after colostrum intake, plasma IgG against KLH, IgM against KLH, growth hormone, IGF-1, insulin, glucose, urea, and NEFA were analyzed, without time effect in the model.

Additionally, variables including birth weight, dam's colostrum yield, total IgG concentration and total IgM concentration in colostrum of calf's dam were analyzed, without time effect in the model.

From weaning to calving. During the rearing period, plasma IgG against KLH, IgM against KLH, growth hormone, IGF-1, insulin, glucose, urea, BHB, NEFA and

body weight were analyzed with a time effect of age in month (mo 3 to 23, 6 time points).

First 100 DIM after calving. During the first 100 DIM after their first calving, plasma IgG against KLH, IgM against KLH, growth hormone, IGF-1, insulin, glucose, urea, BHB, NEFA and body weight were analyzed with a time effect of week in lactation (wk 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14).

Body weight, BCS, and milk fat, milk protein, milk lactose, SCC, milk urea, milk yield, FPCM, were analyzed with a time effect of week in lactation (wk 1 to 14). This analysis included a repeated effect of day in lactation, with heifer as a repeated subject.

Additionally, variables including number of inseminations per pregnancy and age at first calving were analyzed, without time effect in the model. Furthermore, preliminary analysis showed no effect of age at first calving of the heifers on milk performance or any of the plasma variables. For body weight for 100DIM, results are presented with and without 'age at first calving' as a covariable.

RESULTS

In the previous study (Burgers et al., 2021), from the 154 cows that entered the experiment, 127 cows gave birth to calves, with 62 heifer calves and 65 male calves. Insemination per conception of dams for 62 heifer calves yielded CInt_1 vs. CInt_2 vs. CInt_3: 1.5, 2.4, 2.5 (P = 0.10). Fifteen dams did not conceive within 75 d after the planned VWP (9 from VWP50, 4 from VWP125, and 2 from VWP200), leading to a difference between the intended VWP and the actual CInt. The least squares means and range of dam's CInt of the 3 CInt groups is shown per VWP and per CInt in **Table 1**, together with the number of heifer calves in each group. The average lactation length of dams was 322 (±6.36), 391 (±4.09), and 471 (±6.68) d for dams in CInt_1, CInt_2, and CInt_3, respectively. The average dry period length of dams was 38 (±1.35), 42 (±1.27), and 41 (±2.32) d in CInt_1, CInt_2, and CInt_3, respectively. From the 62 heifer calves born, 53 heifer calves started their first lactation. The other 9 calves did not become a heifer due to health issues, of which 1 calf died on the second day of life (from CInt_2, only analyzed in birth weight model), 2 calves left the experiment before weaning (1 from CInt_1, 1 from CInt_3), 1 calf did not reach insemination (from CInt_3), and 5 calves did not reach the end of pregnancy (1 from CInt_1, 1 from CInt_2, 3 from CInt_3). The results of the current study are presented in 3 periods, from birth to weaning, from weaning to calving, and during the first 100DIM. Time profiles for the periods from birth to weaning, from birth to calving, and during the first 100DIM are presented in supplementary figures (**Supplementary Figure S1, S2**).

From Birth to Weaning

Calves from CInt_1 had higher IgG and IgM against KLH in plasma compared with calves from CInt_3 (P < 0.01 and P = 0.05, respectively; **Table 2**). Calves from CInt_1 had higher NEFA concentration in plasma compared with calves from CInt_2 (P = 0.05) or CInt_3 (P < 0.01). There was an interaction between dam's CInt and parity class for IgG against KLH. For calves from primiparous dams, CInt_1 group had greater IgG against KLH (P = 0.01; **Figure 1**) compared with CInt_3. There was an interaction between dam's CInt and parity for plasma growth hormone concentration, but post hoc comparisons were not significant. Moreover, the effect of dam's CInt on IGF-1, insulin, and glucose in calves depended on age of the calf (P < 0.01). Calving interval did not affect birth weight, body weight from birth to weaning, plasma urea concentration in calves (P > 0.05).

Before colostrum intake, plasma variables of calves were not affected by dam's CInt (**Table 3**). However, calves from multiparous dams had greater IgG against KLH (3.41 vs. 2.46, P = 0.03) and IgM against KLH (4.23 vs. 3.08, P = 0.01) in plasma and tended to have lower plasma insulin concentration (11.51 vs. 27.99 U/L, P = 0.07) than calves from primiparous dams.

After colostrum intake, calves from CInt_1 dams tended to have a greater IgG against KLH (P = 0.05) in plasma compared with calves from CInt_3 dams. Calves from multiparous dams tended to have a greater IgG against KLH compared with calves from primiparous dams (8.50 vs. 7.84, P = 0.05).

There was no CInt effect on dam's colostrum yield and total IgG and total IgM concentration in colostrum (**Table 4**). However, multiparous dams had greater total IgG and total IgM concentration in colostrum compared with primiparous dams.

From Weaning to Calving

From weaning to calving, CInt_1-calves tended to have higher plasma NEFA concentration than CInt_3-calves (P = 0.07; **Table 5, Figure 2**). The effect of dam's CInt on urea depended on age of the calf. However, after Tukey correction, there were no significant effects anymore. Besides, there tended to be an interaction between dam's CInt and calf's age on body weight, growth hormone, and IGF-1 (0.05 < P < 0.1). From weaning to calving, there was no effect dam's CInt on IgG and IgM against KLH, insulin, glucose, or BHB concentration in plasma of their offspring. Age affected IgG and IgM against KLH, insu-

Table 2. Body weight, plasma metabolites and hormones from birth to weaning of offspring from dairy cows with different calving interval (CInt) (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d) (LSM ± maximum SEM or CI)[1]

	Calving interval				*P*-value[3]					
Item[2]	CInt_1	CInt_2	CInt_3	SEM(CI)	CInt	Pa	M	CInt × Pa	CInt × M	Pa × M
Birth weight (kg)	37.6	39.6	39.3	1.17	0.34	0.41	NM	0.90	NM	NM
Body weight (kg)	56.3	55.4	56.4	1.57	0.86	0.41	<0.01	0.92	0.19	0.46
IgG against KLH	6.22[a]	5.74[ab]	5.36[b]	0.18	<0.01	<0.01	<0.01	0.04	0.54	0.53
IgM against KLH	6.45[a]	6.31[ab]	5.89[b]	0.17	0.05	<0.01	<0.01	0.08	0.66	0.33
Growth hormone(ng/mL)[4]	8.95	10.25	8.59	(7.31–11.92)	0.25	0.18	<0.01	0.03	0.26	0.90
IGF-1 (ng/mL)	122.58	112.49	106.39	6.46	0.19	0.85	<0.01	0.91	<0.01	0.28
Insulin (U/L)[4]	16.80	15.68	15.09	(12.04–21.23)	0.80	0.44	<0.01	0.16	<0.01	0.32
Glucose (mmol/L)	6.00[a]	5.66[ab]	5.39[b]	0.18	0.02	0.92	<0.01	0.27	<0.01	0.49
Urea (mmol/L)[4]	3.10	3.00	2.95	(2.75–3.33)	0.57	0.63	<0.01	0.28	0.32	0.26
NEFA (mmol/L)[4]	0.34[a]	0.28[b]	0.26[b]	(0.24–0.37)	<0.01	0.19	<0.01	0.12	0.54	0.52

[a, b] Different superscript letters indicate a difference among LSM within the row ($P < 0.05$).

[1]LSM = least squares means. SEM = standard error of the mean. CI = 95% confidence interval.

[2]KLH = Keyhole limpet hemocyanin. IGF-1 = insulin-like growth factor-1. NEFA = nonesterified fatty acids.

[3]Pa = dam's parity class (primiparous or multiparous). M = age in month for the calves. NM means the effect is not in the model.

[4]Transformed data are back transformed, and confidence interval is shown.

*Trend in difference among LSM within the row ($0.05 \leq P < 0.1$).

lin, glucose, and BHB in plasma of the calves, but not plasma NEFA concentration.

First 100 DIM

The average age at first calving of heifer calves and average number of inseminations of heifer calves did not differ among CInt groups (**Table 6,** $P > 0.05$). Heifers from CInt_3 dams had higher body weight than heifers from CInt_1 dams ($P < 0.01$) and heifers from CInt_2 dams ($P < 0.01$), respectively. Moreover, CInt_1-heifers had higher IGF-1 concentration than CInt_2-heifers ($P = 0.04$). CInt_2-heifers tended to have higher plasma urea concentration than CInt_3-heifers ($P = 0.09$). Additionally, heifers from multiparous dams had lower plasma BHB concentration (0.84 vs. 0.94 mmol/L, $P = 0.02$) compared with heifers from primiparous dams.

Effect of dam's CInt on heifer's body weight, IGF-1, insulin and glucose concentrations, depended on dam's parity class ($P \leq 0.05$). Within heifers from primiparous dams, heifers from CInt_3 dams had higher body weight than heifers from CInt_1 dams (572.8 vs. 530.6 kg, $P < 0.01$) or heifers from CInt_2 dams (572.8 vs. 531.8 kg, $P < 0.01$; **Figure 3A**). Moreover, heifers from CInt_2

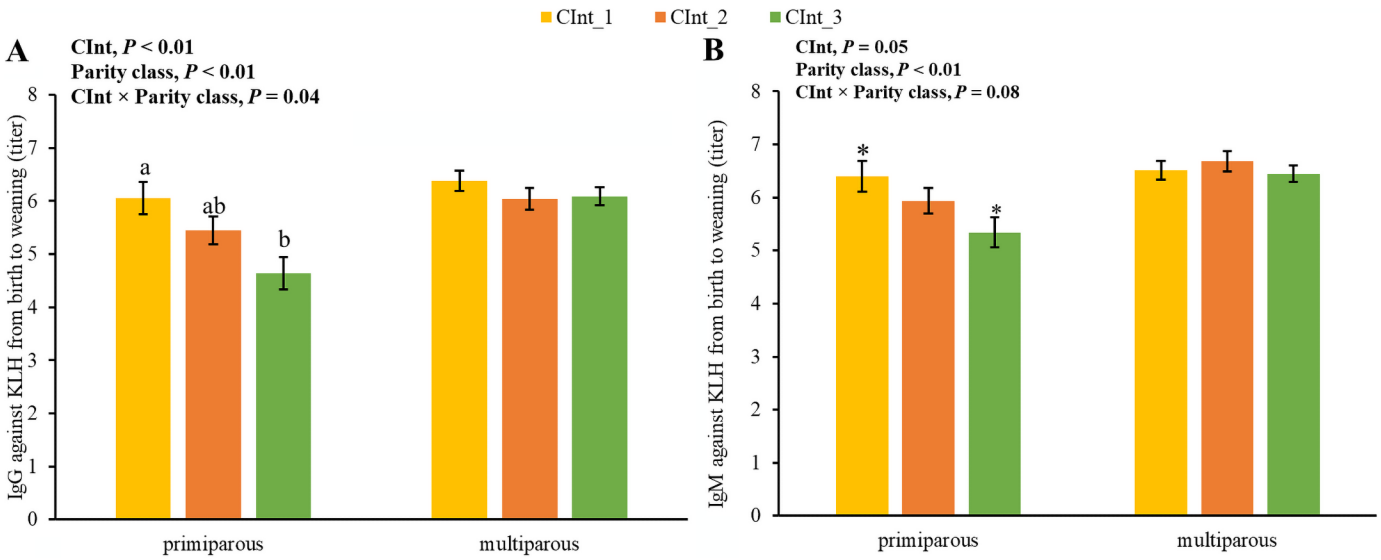

Figure 1. Plasma IgG (A) and IgM (B) against KLH from birth to weaning of offspring from primiparous or multiparous dairy cows with different calving interval (CInt) (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d).

Table 3. Plasma metabolites and hormones at birth before and after colostrum intake of offspring from dairy cows with different calving interval (CInt) (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d) (LSM ± maximum SEM or CI)[1]

	Before colostrum intake				*P*-value[3]			After colostrum intake				*P*-value[3]		
Item[2]	CInt_1	CInt_2	CInt_3	SEM(CI)	CInt	Pa	CInt × Pa	CInt_1	CInt_2	CInt_3	SEM(CI)	CInt	Pa	CInt × Pa
IgG against KLH	3.30	3.05	2.44	0.40	0.25	0.03	0.22	8.74[a]	8.06[ab]	7.71[b]	0.30	0.05	0.05	0.11
IgM against KLH	3.83	3.82	3.33	0.39	0.51	0.01	0.30	8.91	8.28	8.11	0.30	0.13	0.22	0.51
Growth hormone (ng/mL)[4]	11.06	15.18	14.88	(7.33–21.85)	0.44	0.60	0.34	21.73	16.89	18.59	3.48	0.55	0.90	0.16
IGF-1 (ng/mL)	185.87	158.06	169.84	12.08	0.24	0.51	0.42	153.93	154.25	137.80	10.30	0.42	0.80	0.80
Insulin (U/L)[4]	6.23	14.70	13.41	(3.22–11.81)	0.14	0.07	0.46	27.44	32.04	18.47	(6.23–14.02)	0.10	0.49	0.63
Glucose (mmol/L)	4.75	4.36	4.43	0.69	0.89	0.38	0.73	7.18	7.10	6.35	0.37	0.16	0.30	0.82
Urea (mmol/L)	4.42	3.98	3.86	0.27	0.28	0.30	0.36	3.90	4.05	4.39	0.30	0.50	0.26	0.21
NEFA (mmol/L)[4]	0.90	0.79	0.85	0.19	0.91	0.32	0.67	0.50	0.50	0.47	(0.39–0.60)	0.85	0.79	0.67

[a, b] Different superscript letters indicate a difference among LSM within the row ($P < 0.05$).

[1]LSM = least squares means. SEM = standard error of the mean. CI = 95% confidence interval.

[2]KLH = Keyhole limpet hemocyanin. IGF-1 = insulin-like growth factor-1. NEFA = nonesterified fatty acids.

[3]Pa = dam's parity class (primiparous or multiparous).

[4]Transformed data are back transformed, and confidence interval is shown.

*Trend in difference among LSM within the row ($0.05 \leq P < 0.1$).

dams had higher plasma glucose concentration than heifers from CInt_1 dams (3.68 vs. 3.40 mmol/L, $P = 0.02$; **Figure 3B**). In heifers from multiparous dams, CInt_1 had higher IGF-1 concentration than both CInt_2 (118.14 vs. 97.24 ng/mL, $P = 0.03$) and CInt_3 (118.14 vs. 90.77 ng/mL, $P < 0.01$), respectively (**Figure 3C**). Additionally, CInt_2-heifers tended to have higher plasma urea concentration than CInt_3-heifers ($P = 0.09$).

Heifers from dams in CInt_2 had lower FPCM than heifers from dams with CInt_1 ($P < 0.01$) and tended to have lower FPCM than heifers from dams with CInt_3 ($P = 0.08$). Moreover, heifers from CInt_3 dams had lower milk lactose content compared with heifers from CInt_1 ($P < 0.01$) or CInt_2 ($P = 0.01$). Moreover, heifers from CInt_3 dams had lower milk lactose compared with heifers from CInt_1 ($P < 0.01$) or CInt_2 ($P = 0.01$). Effect of dam's CInt on heifer's milk fat, SCC, milk urea concentration and FPCM depended on dam's parity class ($P < 0.05$). Heifers from primiparous dams in CInt_2 had greater SCC compared with CInt_1 (41.48 vs. 25.28 × 10^3 cells/mL, $P < 0.01$) and tended to have greater SCC compared with heifers from primiparous dams in CInt_3 (41.48 vs. 27.80 × 10^3 cells/mL, $P = 0.05$; **Figure 3D**). Heifers from primiparous dams in CInt_2 had lower FPCM than heifers from CInt_1 primiparous dams (28.22 vs. 30.16 kg/d, $P = 0.02$) and heifers from primiparous dams with CInt_3 (28.22 vs. 30.23 kg/d, $P = 0.02$; **Figure 3E**). In heifers from multiparous dams, CInt_3 had lower FPCM than CInt_1 (28.37 vs. 29.92 kg/d, $P = 0.02$). Heifers from CInt_3 dams had higher milk fat content than heifers from CInt_2 dams (4.42 vs. 4.21%, $P = 0.04$; **Figure 3F**). Additionally, heifers from multiparous dams had greater milk lactose content (4.68 vs. 4.64%, $P < 0.01$) and tended to have lower milk urea concentration (20.53 vs. 21.35 mg/dL, $P = 0.08$) compared with heifers from primiparous dams.

During the first 100 DIM, CInt of the dam did not affect heifer's BCS, plasma titers of IgG or IgM against KLH, plasma growth hormone, BHB, or NEFA concentration, or milk yield.

DISCUSSION

The aim of this study was to evaluate the effects of an extended calving interval of dairy cows on their offspring's performance from birth to calving until 100 DIM of their first lactation regarding body condition, metabolic status, and milk performance. Dairy cow's calving interval was extended by a delayed VWP. The actual calving interval was however not only due to the extended VWP, but also due to the period between end of the VWP and actual moment of conception. Almost 25% of the dams (15/62) did not conceive within 75 d after the planned VWP. Possible reasons for this could

Table 4. Colostrum composition and yield of dairy cows with calving interval (CInt) (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d) (LSM ± maximum SEM or CI)[1]

	Calving interval				Parity class			*P*-value[2]		
Item	CInt_1	CInt_2	CInt_3	SEM(CI)	Primiparous	Multiparous	SEM/CI	CInt	Pa	CInt × Pa
Total IgG (mg/mL)	123.92	132.29	130.03	(97.10–163.51)	96.54[b]	171.55[a]	(77.42–196.66)	0.92	<0.01	0.62
Total IgM (mg/mL)	7.02	5.26	5.54	(3.96–9.73)	4.82[b]	7.21[a]	(3.59–8.66)	0.38	0.02	0.62
Yield (kg)	4.93	6.43	4.46	0.72	5.78	4.77	0.68	0.11	0.22	0.21

[a, b] Different superscript letters indicate a difference among LSM within the row ($P < 0.05$).

[1]LSM = least squares means. SEM = standard error of the mean. CI = 95% confidence interval.

[2]Pa = dam's parity class (primiparous or multiparous).

be anestrous, improper timing of insemination (Cordoba and Fricke, 2001, Drake et al., 2020); compromised quality of the semen used in artificial insemination (Koch et al., 2022); compromised oocyte quality (Mokhtari et al., 2016); or improper artificial insemination techniques. Therefore, there was some variation in CInt at a given VWP. This is the reason why effects of CInt were studied and not the effect of VWP.

In the current study, effects of CInt of the dam were even presented when the offspring was lactating. This long-lasting effects of maternal factors align with the Barker hypothesis concerning fetal programming (Barker, 1990), where metabolic status or disease in offspring's adult life can be traced back to the prenatal environment, also known as the developmental origins of health and disease hypothesis (Barker, 2007, Fleming et al., 2015).

At birth, body weight did not differ among calves born to dams with different CInt, possibly related with the similar NEFA concentrations observed in dams with different CInt in last 2 wk before calving (Burgers et al., 2023). This aligns with the findings of Ling et al. (2018), which indicated a negative correlation between calves' birth weight and their dams' NEFA concentration before calving. Natural antibodies are commonly considered as a first-line of defense against pathogens (Maddur et al., 2020). At birth, there were no differences among 3 CInt categories in terms of IgG or IgM against KLH. This is expected as the amount of antibodies that the fetus could get through the placenta is limited because of the placenta structure in ruminants (Baintner, 2007). Directly after colostrum intake, but also during the complete period from birth till weaning at 12 weeks of age, calves born to dams in CInt_1 had more IgG against KLH in plasma than those from CInt_3. Moreover, CInt_1-calves also had more IgM against KLH than CInt_3-calves from birth till weaning. It may be that cows with a long CInt were at a more advanced stage of lactation while conceiving. A higher demand for milk production in dams with the shortest CInt during pregnancy (Huzzey et al., 2005) render them more susceptible to infections and metabolic ailments (Goff and Horst, 1997). This may result in more antibodies in cow's blood and colostrum. In addition, the difference in natural antibody titers in calf's plasma but not in total IgG and IgM concentrations in dam's colostrum could be related to the study by Blecha et al. (1981), which showed the dam affects the calf's intestinal absorption. In the current study, the contrast among CInt classes for IgG or IgM against KLH disappeared during the period from weaning to the offspring's first calving moment. Similarly, Cuttance et al. (2019) also found the difference in passive transfer of immunity on mortality up to 12 mo of age, which disappeared after 12 mo of age and did not adversely affect productivity, performance, or mortality beyond 12 mo of age in heifers. Maternal antibodies provide very good protection for calves until 17 weeks after birth, as immunological maturity is not acquired in calves until 4 or 5 mo of age (Heath et al., 2012).

Calves from cows with the shortest CInt had higher NEFA than the other 2 groups from birth to weaning.

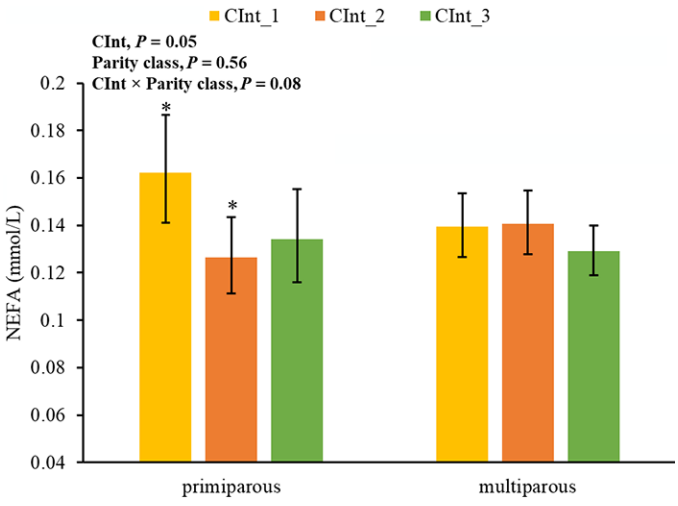

Figure 2. Nonesterified fatty acids (NEFA) of offspring from weaning to calving from primiparous or multiparous dairy cows with different calving interval (CInt) (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d).

Table 5. Body weight, plasma metabolites and hormones of offspring from weaning to calving from dairy cows with different calving interval (CInt) (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d) (LSM ± maximum SEM or CI)[1]

	Calving interval				*P*-value[3]					
Item[2]	CInt_1	CInt_2	CInt_3	SEM(CI)	CInt	Pa	M	CInt × Pa	CInt × M	Pa × M
Body weight (kg)	336.9	331.5	340.7	7.35	0.51	0.91	<0.01	0.10	0.06	0.02
IgG against KLH	7.10	7.26	6.90	0.22	0.34	0.44	<0.01	0.68	0.47	0.50
IgM against KLH	7.84	7.84	7.58	0.18	0.37	0.31	<0.01	0.61	0.39	0.59
Growth hormone (ng/mL)[4]	3.25	3.78	3.43	(2.78–4.38)	0.38	0.09	<0.01	0.19	0.08	0.78
IGF-1 (ng/mL)	178.28	171.35	172.73	7.84	0.77	0.91	<0.01	0.89	0.09	0.78
Insulin (U/L)	21.04	18.58	19.78	1.35	0.41	0.93	<0.01	0.42	0.18	0.67
Glucose (mmol/L)	4.48	4.43	4.36	0.06	0.38	0.12	<0.01	0.85	0.11	0.87
Urea (mmol/L)	3.54	3.62	3.46	0.13	0.66	0.76	<0.01	0.22	0.02	0.92
BHB (mmol/L)	0.42	0.39	0.42	0.02	0.45	0.26	<0.01	0.36	0.20	0.99
NEFA (mmol/L)[4]	0.150*	0.133	0.131*	(0.121–0.164)	0.05	0.56	0.19	0.08	0.93	0.78

[1]LSM = least squares means. SEM = standard error of the mean. CI = 95% confidence interval.

[2]KLH = Keyhole limpet hemocyanin. IGF-1 = insulin-like growth factor-1. BHB = β-hydroxybutyrate. NEFA = nonesterified fatty acids.

[3]Pa = dam's parity class (primiparous or multiparous). M = age in month for the calves.

[4]Data are back transformed, and confidence interval is shown.

Based on previous studies (Grummer, 1993, LeBlanc, 2006), nonesterified fatty acids reflect the magnitude of mobilization of fat from storage, this is possibly related to the higher plasma BHB concentration of dams with shortest VWP during last 2 wk before calving (Burgers et al., 2023). Moreover, dams with the shortest CInt produced more milk during their pregnancy, and their pregnancy overlapped more with higher daily milk production than that of dams with longer CInt (Burgers et al., 2021). This means that the fetus competes for nutrients

Table 6. Reproductive performance before first calving, and body condition, milk performance, plasma metabolites and hormones after calving until 100 d in milk of offspring from dairy cows with different calving interval (CInt) (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d) (LSM ± maximum SEM or CI)[1]

	Calving interval				*P*-value[3]					
Item[2]	CInt_1	CInt_2	CInt_3	SEM(CI)	CInt	Pa	W	CInt × Pa	CInt × W	Pa × W
Inseminations per pregnancy	1.4	1.4	1.4	0.19	0.95	0.52	NM	0.83	NM	NM
Age at first calving (month)	24.9	24.8	25.3	0.46	0.68	0.92	NM	0.90	NM	NM
Body weight (kg)	544.3[b]	536.4[b]	563.9[a]	7.86	<0.01	0.23	0.21	<0.01	1.00	0.98
BCS	3.3	3.3	3.3	0.06	0.79	0.84	<0.01	0.66	1.00	0.89
IgG against KLH	7.10	6.69	7.15	0.27	0.27	0.20	0.32	0.31	0.71	0.15
IgM against KLH	7.80	7.70	8.04	0.20	0.36	0.26	0.89	0.84	0.86	0.10
Growth hormone (ng/mL)[4]	3.04	3.45	3.67	(2.57–4.38)	0.22	0.67	<0.01	0.55	0.39	0.70
IGF-1 (ng/mL)	111.53[a]	97.68[b]	100.90[ab]	5.94	0.04	0.58	<0.01	0.01	0.32	0.73
Insulin (U/L)[4]	15.18	17.04	16.71	(2.04–2.72)	0.42	0.78	<0.01	0.02	0.72	0.81
Glucose (mmol/L)	3.53	3.59	3.48	0.05	0.14	0.32	0.10	<0.01	0.35	0.16
Urea (mmol/L)	3.30	3.52*	3.24*	0.11	0.08	0.19	<0.01	0.60	0.35	0.60
BHB (mmol/L)[4]	0.87	0.90	0.90	(0.78–1.00)	0.83	0.02	0.01	0.83	0.59	0.34
NEFA (mmol/L)[4]	0.21	0.19	0.20	(0.17–0.23)	0.40	0.49	<0.01	0.20	0.79	0.71
Milk										
Yield (kg)	25.02	23.26	24.56	1.22	0.49	0.92	<0.01	0.34	0.99	0.97
Fat (%)	4.26	4.33	4.37	0.07	0.23	0.28	<0.01	0.01	0.81	0.19
Protein (%)[4]	3.34	3.37	3.31	(3.23–3.45)	0.47	0.69	<0.01	0.09	0.02	1.00
Lactose (%)	4.68[a]	4.67[a]	4.63[b]	0.02	<0.01	<0.01	<0.01	0.30	0.64	<0.01
SCC (× 10^3 cells/mL)[4]	30.60	34.79	32.01	(27.13–38.74)	0.27	0.13	<0.01	<0.01	0.85	0.81
Urea (%)	21.08	21.22	20.52	0.58	0.42	0.08	<0.01	0.02	0.73	0.86
FPCM (kg/d)	30.04[a]	28.45[b*]	29.30*	0.55	<0.01	0.11	<0.01	0.01	0.95	0.70

[a, b] Different superscript letters indicate a difference among LSM within the row ($P < 0.05$).

[1]LSM = least squares means. SEM = standard error of the mean. CI = 95% confidence interval.

[2]BCS = body condition score. SCC = somatic cell count. FPCM = fat- and protein-corrected milk (CVB, 2012). KLH = Keyhole limpet hemocyanin. IGF-1 = insulin-like growth factor-1. BHB = β-hydroxybutyrate. NEFA = nonesterified fatty acids.

[3]Pa = dam's parity class (primiparous or multiparous). W = week in lactation for the heifer calves. NM means the effect is not in the model.

[4]Data are back transformed, and confidence interval is shown.

*Trend in difference among LSM within the row ($0.05 \leq P < 0.1$).

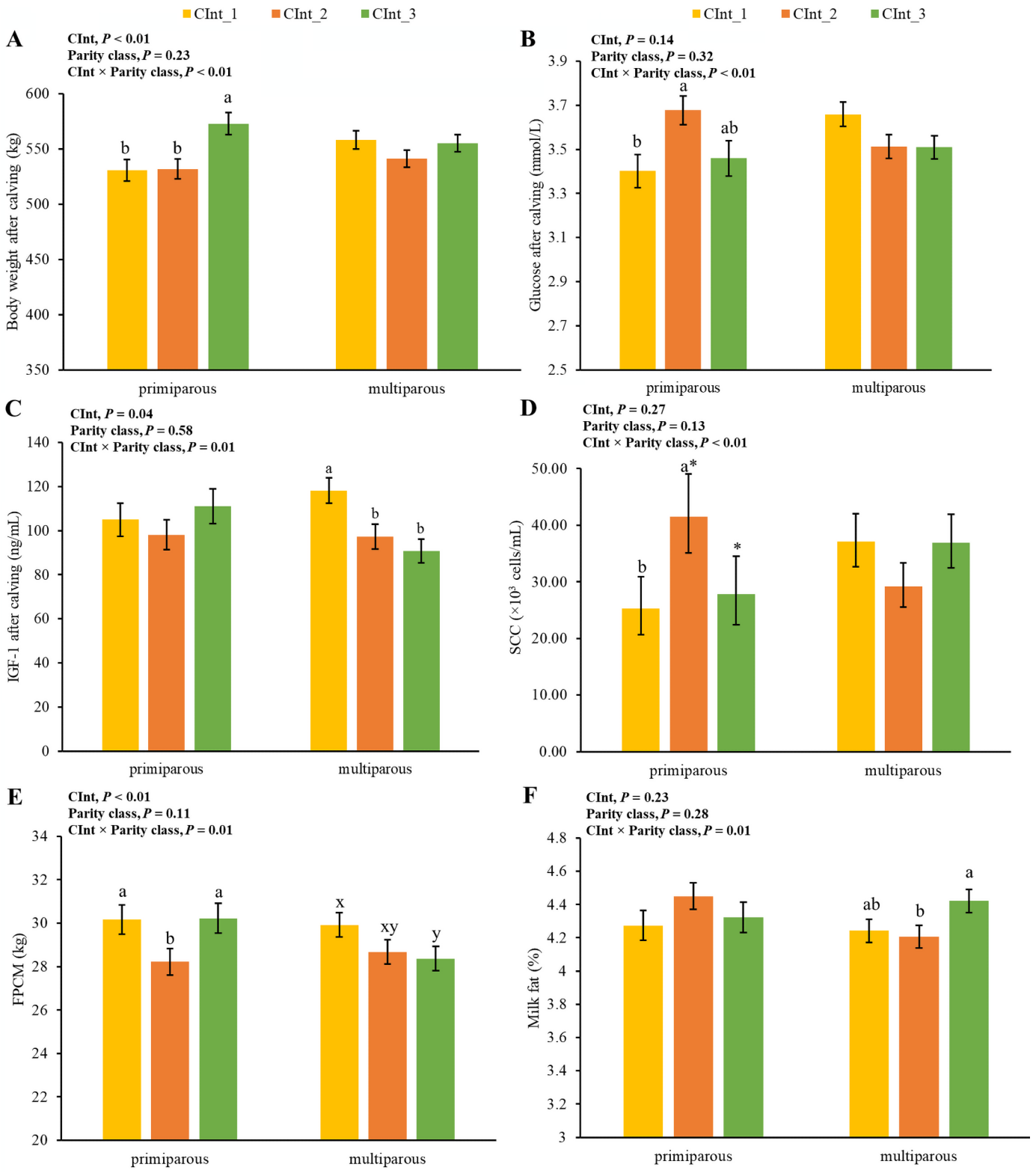

Figure 3. Body weight (A), plasma glucose (B), IGF-1 (C), milk somatic cell count (SCC, D), fat and protein corrected milk yield (FPCM, E), and milk fat (F) during the first 100 DIM after calving of offspring from primiparous or multiparous dairy cows with different calving interval (CInt) (CInt_1: 324 - 408 d; CInt_2: 409 - 468 d; CInt_3: 469 - 586 d).

with the requirements for milk production, assuming that energy intake is the same in all CInt groups. More specifically, cows with a short VWP were mobilizing body reserves during the breeding period, while cows with a VWP of 125 or 200 d were gaining body weight during their breeding period (Ma et al., 2022a). This implies that for the early developing embryo energy status of the dam differs between an early and delayed breeding period.

After weaning until calving, limited effects of dam's CInt were found on body condition or metabolism, except for a tendency of higher NEFA in CInt_1-calves than CInt_3-calves. As calves grow and develop, differences in early calves gradually stabilized in terms of their physical condition and metabolism, showing no differences among CInt categories during the later rearing period, compared with the period before weaning. In line with the present study, Monteiro et al. (2016) also stated differences in body weight of calves disappeared in their later life, indicating that, over time, calves from different maternal conditions ultimately reached similar body conditions. However, in our study, the difference in body weight appeared among those heifer calves again after their first calving. Additionally, from birth until calving, concentrations of plasma hormones, including growth hormone, IGF-1, and insulin, did not differ among groups in terms of dam's CInt. This indicates that delayed insemination method for dams per se did not affect endocrine system during calves' early life. However, hormone secretion and production involved in the metabolism regulation in neonates depend on the developmental stage and feeding response. It is likely that endocrine action in neonates is not fully established and, therefore, requires postnatal maturation (Hammon et al., 2012). In line with the postnatal maturation, we found effects on IGF-1 after calving.

During the first 100 DIM after calving, a longer CInt in primiparous dams resulted in heifer's greater body weight. In multiparous dams, a longer CInt resulted in heifer's lower FPCM, greater milk fat content and lower plasma IGF-1. Heifers born to multiparous dams in CInt_3 had a greater milk fat content than heifers in the other 2 groups, the difference disappeared when we corrected milk fat content for milk yield. This difference in percentage could also be related to the more days of pregnancy in late lactation for those dams that had an extended CInt. More pregnancy days in late lactation of dams in longer CInt was related to more pregnancy days with lower milk yield (Burgers et al., 2021), potentially resulted in more energy partitioning toward both maternal body weight (Bauman and Bruce Currie, 1980) and fetal development (Marett et al., 2019). After calving, heifers from CInt_3 dams had the highest body weight, when we put age at first calving as a covariable, CInt_1-heifers were the heaviest. This change was precisely in line with an earlier study (Han et al., 2021), where age at first calving positively impacted postpartum body weight. However, we did not find big changes on milk yield with age at first calving as a covariable, in line with earlier studies (Ettema and Santos, 2004, Han et al., 2021), concluding that maturation rate was not a primary contributor to variation in milk yield. Additionally, those heifers from CInt_1 primiparous dams had higher FPCM during the first 100 DIM than CInt_2. The higher FPCM aligns with lower glucose concentrations in plasma. Similarly, heifers from primiparous CInt_2 dams had lower FPCM, and higher plasma glucose. Lower FPCM can be explained by altered metabolism because calves experienced different metabolic status in utero (Monteiro et al., 2016). As observed in our earlier studies, longer VWP reduced milk yield within 6 wk (Burgers et al., 2023) and 9 wk relative to dry-off (Ma et al., 2022b), potentially partitioning more energy toward the fetus. Heifers from primiparous dams in CInt_2 had greater SCC concentration. When taking daily milk yield into account to calculate the daily total SCC secreted, there was only a tendency in daily total SCC between heifers from CInt_2 and CInt_3 in multiparous dams (878.93 vs. 1200.51 $\times$ 10^3 cells/day, $P = 0.08$). This indicated that SCC differences among CInt groups could at least partly be explained by differences in milk yield, with a greater SCC for heifers from CInt_2 dams which also produced less milk. Moreover, in accordance with the study by Mullen et al. (2011), where plasma IGF-1 concentration is positively related to milk yield, and 2 IGF genes were associated with decreased milk fat content due to the important role that IGF-1 plays in mammary gland growth and function (Akers, 2006). Although biologically and practically interesting, the interaction effects between CInt and parity should be interpreted with caution. In multiparous cows, animal numbers ranged from 13 to 18 per CInt group. In primiparous cows, however, animal numbers ranged from 5 to 7 per CInt group. Especially the CInt effects observed in primiparous cows, but not in multiparous cows, require further investigation. While these sample sizes are not unusual in long-term calf studies (Willett et al., 1982, Wilson et al., 2017, Guadagnin et al., 2024) and the statistical method used included a correction for multiple comparisons, future studies are needed to confirm these trends.

Not only CInt, but also dam characteristics like milk yield, metabolic status, disease or fertility around conception or during pregnancy can be hypothesized to affect health and performance of offspring. Our future work aims to investigate in more detail the relationship between metabolism, fertility, performance of dams and growth, development, metabolism, and milk performance of their offspring. Moreover, although growing number of studies indicate that an extended CInt can be

of interest to manage health and fertility in dairy cows (Österman and Bertilsson, 2003, Burgers et al., 2021), the current results indicate that consequences for their calves should be considered. Future studies should evaluate consequences for both dairy and veal calves, as well as consequences of a customized lactation length, based on individual cow characteristics, for calf health and development to support implementation of deliberately extended calving intervals in practice.

CONCLUSION

In conclusion, calves born from dams with an extended calving interval differ in natural antibodies, body weight, and milk performance across different periods from birth until the first 100 DIM. More differences among CInt groups in immune variables were observed before weaning, and more in body weight, and milk production variables occurred after calving. A longer calving interval in dams, resulted in heifer calves with lower IgG and IgM levels against KLH and lower plasma NEFA concentration during the first 12 weeks of life. While during the first 100 DIM of the offspring's first lactation, a longer calving interval in dams resulted in heifers with greater body weight and lower milk production. This is one of the first studies that evaluated the effects of dam's calving interval on offspring's performance. Although we found some consequences of CInt in terms of immunity during early life and milk production during later life, results need to be confirmed in further studies.

ACKNOWLEDGMENTS

The authors thank the China Scholarship Council for financial support of the PhD study of the first author. The authors thank the staff of the Dairy Campus research farm (Leeuwarden, the Netherlands) for their work and dedication during the experiment. This study was financed by Dutch dairy cattle fund (Melkveefonds, Wageningen, the Netherlands) and Samenwerkingsverband Noord-Nederland (SNN), Ruimtelijk Economisch Programma. The authors state no conflicts of interest.

REFERENCES

Akers, R. M. 2006. Major advances associated with hormone and growth factor regulation of mammary growth and lactation in dairy cows. J. Dairy Sci. 89:1222–1234. https://doi.org/10.3168/jds.S0022-0302(06)72191-9.

Baintner, K. 2007. Transmission of antibodies from mother to young: Evolutionary strategies in a proteolytic environment. Vet. Immunol. Immunopathol. 117:153–161. https://doi.org/10.1016/j.vetimm.2007.03.001.

Barker, D. J. 1990. The fetal and infant origins of adult disease. BMJ 301:1111. https://doi.org/10.1136/bmj.301.6761.1111.

Barker, D. J. 2007. The origins of the developmental origins theory. J. Intern. Med. 261:412–417. https://doi.org/10.1111/j.1365-2796.2007.01809.x.

Bauman, D. E., and W. Bruce Currie. 1980. Partitioning of nutrients during pregnancy and lactation: A review of mechanisms involving homeostasis and homeorhesis. J. Dairy Sci. 63:1514–1529. https://doi.org/10.3168/jds.S0022-0302(80)83111-0.

Berry, D. P., P. Lonergan, S. T. Butler, A. R. Cromie, T. Fair, F. Mossa, and A. C. O. Evans. 2008. Negative influence of high maternal milk production before and after conception on offspring survival and milk production in dairy cattle. J. Dairy Sci. 91:329–337. https://doi.org/10.3168/jds.2007-0438.

Blecha, F., R. C. Bull, D. P. Olson, R. H. Ross, and S. Curtis. 1981. Effects of prepartum protein restriction in the beef cow on immunoglobin content in blood and colostral whey and subsequent immunoglobin absorption by the neonatal calf2. J. Anim. Sci. 53:1174–1180. https://doi.org/10.2527/jas1981.5351174x.

Bossaert, P., E. Fransen, A. Langbeen, M. Stalpaert, I. Vandenbroeck, P. E. Bols, and J. L. Leroy. 2014. Effects of parity and periconceptional metabolic state of holstein–friesian dams on the glucose metabolism and conformation in their newborn calves. Animal 8:975–981. https://doi.org/10.1017/S1751731114000706.

Burgers, E. E. A., R. M. A. Goselink, R. M. Bruckmaier, J. J. Gross, R. Jorritsma, B. Kemp, A. Kok, and A. T. van Knegsel. 2023. Effect of voluntary waiting period on metabolism of dairy cows during different phases of the lactation. J. Anim. Sci. 101:skad194. https://doi.org/10.1093/jas/skad194.

Burgers, E. E. A., A. Kok, R. M. A. Goselink, H. Hogeveen, B. Kemp, and A. T. M. van Knegsel. 2021. Effects of extended voluntary waiting period from calving until first insemination on body condition, milk yield, and lactation persistency. J. Dairy Sci. 104:8009–8022. https://doi.org/10.3168/jds.2020-19914.

Carcea, I., N. L. Caraballo, B. J. Marlin, R. Ooyama, J. S. Riceberg, J. M. Mendoza Navarro, M. Opendak, V. E. Diaz, L. Schuster, M. I. Alvarado Torres, H. Lethin, D. Ramos, J. Minder, S. L. Mendoza, C. J. Bair-Marshall, G. H. Samadjopoulos, S. Hidema, A. Falkner, D. Lin, A. Mar, Y. Z. Wadghiri, K. Nishimori, T. Kikusui, K. Mogi, R. M. Sullivan, and R. C. Froemke. 2021. Oxytocin neurons enable social transmission of maternal behaviour. Nature 596:553–557. https://doi.org/10.1038/s41586-021-03814-7.

Carvalho, M. R., C. Aboujaoude, F. Peñagaricano, J. E. P. Santos, T. J. DeVries, B. W. McBride, and E. S. Ribeiro. 2020. Associations between maternal characteristics and health, survival, and performance of dairy heifers from birth through first lactation. J. Dairy Sci. 103:823–839. https://doi.org/10.3168/jds.2019-17083.

Cordoba, M. C., and P. M. Fricke. 2001. Evaluation of two hormonal protocols for synchronization of ovulation and timed artificial insemination in dairy cows managed in grazing-based dairies. J. Dairy Sci. 84:2700–2708. https://doi.org/10.3168/jds.S0022-0302(01)74724-8.

Cuttance, E. L., W. A. Mason, R. A. Laven, and C. V. C. Phyn. 2019. Relationships between failure of passive transfer and subsequent mortality, bodyweights and lactation performance in 12–36 month old heifers on pasture-based, seasonal calving dairy farms in new zealand. Vet. J. 251:105348. https://doi.org/10.1016/j.tvjl.2019.105348.

CVB. 2016. Cvb tabellenboek veevoeding (feedstuff table 2016). CVB, the Netherlands: Centraal Veevoeder Bureau Lelystad.

de Koning, D. B., E. P. C. W. Damen, M. G. B. Nieuwland, E. M. van Grevenhof, W. Hazeleger, B. Kemp, and H. K. Parmentier. 2015. Association of natural (auto-) antibodies in young gilts with osteochondrosis at slaughter. Livest. Sci. 176:152–160. https://doi.org/10.1016/j.livsci.2015.03.017.

Donovan, D. C., A. J. Reber, J. D. Gabbard, M. Aceves-Avila, K. L. Galland, K. A. Holbert, L. O. Ely, and D. J. Hurley. 2007. Effect of maternal cells transferred with colostrum on cellular responses to pathogen antigens in neonatal calves. Am. J. Vet. Res. 68:778–782. https://doi.org/10.2460/ajvr.68.7.778.

Drake, E., S. A. Holden, V. Aublet, R. C. Doyle, C. Millar, S. G. Moore, C. Maicas, F. Randi, A. R. Cromie, P. Lonergan, and S. T. Butler. 2020. Evaluation of delayed timing of artificial insemination with sex-sorted sperm on pregnancy per artificial insemination in

seasonal-calving, pasture-based lactating dairy cows. J. Dairy Sci. 103:12059–12068. https://doi.org/10.3168/jds.2020-18847.

Ettema, J. F., and J. E. P. Santos. 2004. Impact of age at calving on lactation, reproduction, health, and income in first-parity holsteins on commercial farms. J. Dairy Sci. 87:2730–2742. https://doi.org/10.3168/jds.S0022-0302(04)73400-1.

Ferguson, J. D., D. T. Galligan, and N. Thomsen. 1994. Principal descriptors of body condition score in holstein cows. J. Dairy Sci. 77:2695–2703. https://doi.org/10.3168/jds.S0022-0302(94)77212-X.

Fleming, T. P., M. A. Velazquez, and J. J. Eckert. 2015. Embryos, dohad and david barker. J. Dev. Orig. Health Dis. 6:377–383. https://doi.org/10.1017/S2040174415001105.

Gaillard, C., T. Kristensen, L. B. Larsen, J. O. Lehmann, G. M. Maciel, L. Mogensen, N. A. Poulsen, J. Sehested, M. Vestergaard, and M. R. Weisbjerg. 2019. Review: Extended lactation in dairy cattle. Animal 13(S1):s65–s74. https://doi.org/10.1017/S1751731119000806.

Goff, J., and R. 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.

Grummer, R. R. 1993. Etiology of lipid-related metabolic disorders in periparturient dairy cows. J. Dairy Sci. 76:3882–3896. https://doi.org/10.3168/jds.S0022-0302(93)77729-2.

Guadagnin, A. R., F. Peñagaricano, G. E. Dahl, and J. Laporta. 2024. Programming effects of intrauterine hyperthermia on adrenal gland development. J. Dairy Sci. https://doi.org/10.3168/jds.2023-24606.

Hammon, H. M., J. Steinhoff-Wagner, U. Schönhusen, C. C. Metges, and J. W. Blum. 2012. Energy metabolism in the newborn farm animal with emphasis on the calf: Endocrine changes and responses to milk-born and systemic hormones. Domest. Anim. Endocrinol. 43:171–185. https://doi.org/10.1016/j.domaniend.2012.02.005.

Han, L., A. J. Heinrichs, A. De Vries, and C. D. Dechow. 2021. Relationship of body weight at first calving with milk yield and herd life. J. Dairy Sci. 104:397–404. https://doi.org/10.3168/jds.2020-19214.

Heath, D. D., C. Robinson, and M. W. Lightowlers. 2012. Maternal antibody parameters of cattle and calves receiving eg95 vaccine to protect against echinococcus granulosus. Vaccine 30:7321–7326. https://doi.org/10.1016/j.vaccine.2012.08.076.

Huzzey, J. M., M. A. G. von Keyserlingk, and D. M. Weary. 2005. Changes in feeding, drinking, and standing behavior of dairy cows during the transition period. J. Dairy Sci. 88:2454–2461. https://doi.org/10.3168/jds.S0022-0302(05)72923-4.

Jarman, J., J. Kay, M. Neal, D. Donaghy, and P. Tozer. 2020. Implications of using an extended lactation to change from a spring-calving to an autumncalving farm system in south taranaki. New Zealand Journal of Animal Science and Production 80:143–149.

Kamal, M. M., M. Van Eetvelde, E. Depreester, M. Hostens, L. Vandaele, and G. Opsomer. 2014. Age at calving in heifers and level of milk production during gestation in cows are associated with the birth size of holstein calves. J. Dairy Sci. 97:5448–5458. https://doi.org/10.3168/jds.2014-7898.

Koch, J., L. P. Weber, M. Heppelmann, F. Freise, M. Klingelmann, and L. Bachmann. 2022. Effect of different thawing methods for frozen bull semen and additional factors on the conception rate of dairy cows in artificial insemination. Animals (Basel) 12:2330. https://doi.org/10.3390/ani12182330.

Latouche, C., S. E. Heywood, S. L. Henry, M. Ziemann, R. Lazarus, A. El-Osta, J. A. Armitage, and B. A. Kingwell. 2014. Maternal overnutrition programs changes in the expression of skeletal muscle genes that are associated with insulin resistance and defects of oxidative phosphorylation in adult male rat offspring1, 2, 3. J. Nutr. 144:237–244. https://doi.org/10.3945/jn.113.186775.

LeBlanc, S. 2006. Monitoring programs for transition dairy cows. in Proceedings of the 26th World Biuatrics Congress. Nice.

Lee, H.-S. 2015. Impact of maternal diet on the epigenome during in utero life and the developmental programming of diseases in childhood and adulthood. Nutrients 7:9492–9507. https://doi.org/10.3390/nu7115467.

Ling, T., M. Hernandez-Jover, L. M. Sordillo, and A. Abuelo. 2018. Maternal late-gestation metabolic stress is associated with changes in immune and metabolic responses of dairy calves. J. Dairy Sci. 101:6568–6580. https://doi.org/10.3168/jds.2017-14038.

Lopes, M. G., A. S. Alharthi, V. Lopreiato, E. Abdel-Hamied, Y. Liang, D. N. Coleman, H. Dai, M. N. Corrêa, M. T. Socha, M. A. Ballou, E. Trevisi, and J. J. Loor. 2021. Maternal supplementation with cobalt sources, folic acid, and rumen-protected methionine and its effects on molecular and functional correlates of the immune system in neonatal holstein calves. J. Dairy Sci. 104:9340–9354. https://doi.org/10.3168/jds.2020-19674.

Ma, J., E. E. A. Burgers, A. Kok, R. M. A. Goselink, T. J. G. M. Lam, B. Kemp, and A. T. M. van Knegsel. 2022a. Consequences of extending the voluntary waiting period for insemination on reproductive performance in dairy cows. Anim. Reprod. Sci. 244:107046. https://doi.org/10.1016/j.anireprosci.2022.107046.

Ma, J., A. Kok, R. M. A. Goselink, T. J. G. M. Lam, B. Kemp, and A. T. M. van Knegsel. 2022b. Udder health of dairy cows with an extended voluntary waiting period from calving until the first insemination. J. Dairy Res. 89:271–278. https://doi.org/10.1017/S0022029922000516.

Maddur, M. S., S. Lacroix-Desmazes, J. D. Dimitrov, M. D. Kazatchkine, J. Bayry, and S. V. Kaveri. 2020. Natural antibodies: From first-line defense against pathogens to perpetual immune homeostasis. Clin. Rev. Allergy Immunol. 58:213–228. https://doi.org/10.1007/s12016-019-08746-9.

Marett, L. C., M. J. Auldist, W. J. Wales, K. L. Macmillan, F. R. Dunshea, and B. J. Leury. 2019. Responses to metabolic challenges in dairy cows with high or low milk yield during an extended lactation. J. Dairy Sci. 102:4590–4605. https://doi.org/10.3168/jds.2018-15513.

Mayasari, N., G. de Vries Reilingh, M. G. B. Nieuwland, G. J. Remmelink, H. K. Parmentier, B. Kemp, and A. T. M. van Knegsel. 2015. Effect of maternal dry period length on colostrum immunoglobulin content and on natural and specific antibody titers in calves. J. Dairy Sci. 98:3969–3979. https://doi.org/10.3168/jds.2014-8753.

Mokhtari, A., M. Kafi, M. J. Zamiri, and R. Akbari. 2016. Factors affecting the size of ovulatory follicles and conception rate in high-yielding dairy cows. Theriogenology 85:747–753. https://doi.org/10.1016/j.theriogenology.2015.10.020.

Monteiro, A. P. A., S. Tao, I. M. T. Thompson, and G. E. Dahl. 2016. In utero heat stress decreases calf survival and performance through the first lactation. J. Dairy Sci. 99:8443–8450. https://doi.org/10.3168/jds.2016-11072.

Mullen, M., D. Berry, D. Howard, M. Diskin, C. Lynch, L. Giblin, D. Kenny, D. Magee, K. Meade, and S. Waters. 2011. Single nucleotide polymorphisms in the insulin-like growth factor 1 (igf-1) gene are associated with performance in holstein-friesian dairy cattle. Front. Genet. 2. https://doi.org/10.3389/fgene.2011.00003.

Niozas, G., G. Tsousis, I. Steinhöfel, C. Brozos, A. Römer, S. Wiedemann, H. Bollwein, and M. Kaske. 2019. Extended lactation in high-yielding dairy cows. I. Effects on reproductive measurements. J. Dairy Sci. 102:799–810. https://doi.org/10.3168/jds.2018-15115.

Österman, S., and J. Bertilsson. 2003. Extended calving interval in combination with milking two or three times per day: Effects on milk production and milk composition. Livest. Prod. Sci. 82:139–149. https://doi.org/10.1016/S0301-6226(03)00036-8.

van Emon, M. L., C. S. Schauer, L. A. Lekatz, S. R. Eckerman, K. Maddock-Carlin, and K. A. Vonnahme. 2014. Supplementing metabolizable protein to ewes during late gestation: I. Effects on ewe performance and offspring performance from birth to weaning1. J. Anim. Sci. 92:339–348. https://doi.org/10.2527/jas.2013-6851.

van Knegsel, A. T. M., E. E. A. Burgers, J. Ma, R. M. A. Goselink, and A. Kok. 2022. Extending lactation length: Consequences for cow, calf, and farmer. J. Anim. Sci. 100:skac220. https://doi.org/10.1093/jas/skac220.

Vicari, T., J. J. van den Borne, W. J. Gerrits, Y. Zbinden, and J. W. Blum. 2008. Postprandial blood hormone and metabolite concentrations influenced by feeding frequency and feeding level in veal calves. Domest. Anim. Endocrinol. 34:74–88. https://doi.org/10.1016/j.domaniend.2006.11.002.

Wallace, J. M., J. S. Milne, B. W. Aitken, R. P. Aitken, and C. L. Adam. 2020. Ovine prenatal growth-restriction and sex influence fetal adipose tissue phenotype and impact postnatal lipid metabolism and

adiposity in vivo from birth until adulthood. PLoS One 15:e0228732. https://doi.org/10.1371/journal.pone.0228732.

Willett, L. B., H. I. Durst, T. T. Y. Liu, F. L. Schanbacher, and P. D. Moorhead. 1982. Performance and health of offspring of cows experimentally exposed to polybrominated biphenyls. J. Dairy Sci. 65:81–91. https://doi.org/10.3168/jds.S0022-0302(82)82156-5.

Wilson, M. L., S. R. McCoski, A. J. Geiger, R. M. Akers, S. E. Johnson, and A. D. Ealy. 2017. The influence of postnatal nutrition on reproductive tract and endometrial gland development in dairy calves. J. Dairy Sci. 100:3243–3256. https://doi.org/10.3168/jds.2016-11880.

ORCIDS

Yapin Wang https://orcid.org/0000-0001-8658-3646
Allyson Ipema https://orcid.org/0000-0003-3071-0743
Roselinde Goselink https://orcid.org/0000-0002-1610-0546
Eline Burgers https://orcid.org/0000-0002-1586-1570
Josef Gross https://orcid.org/0000-0002-2578-6076
Rupert Bruckmaier https://orcid.org/0000-0002-9374-5890
Bas Kemp https://orcid.org/0000-0002-9765-9105
Ariette van Knegsel https://orcid.org/0000-0003-1959-3363