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Associations between maternal characteristics and health, survival, and performance of dairy heifers from birth through first lactation

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ABSTRACT

The objective of this study was to investigate whether health, survival, and performance of dairy heifers from birth through first lactation are associated with parity and health status of their dams. Holstein heifers (n = 1,811) derived from artificial insemination were categorized as (1) daughters of primiparous cows that, consequently, were nonlactating heifers during gestation (Prim-NoL; n = 787); (2) daughters of multiparous cows that did not have any clinical diseases in the previous lactation (Mult-NoCD; n = 638); and (3) daughters of multiparous cows that had at least one clinical disease in the previous lactation (Mult-CD; n = 386). Clinical diseases of the multiparous dams included retained placenta, metritis, mastitis, lameness, and digestive and respiratory problems. Data collected for evaluation of daughters included genotypic and phenotypic characteristics at birth, morbidity, reproductive performance, and culling from birth through 305 d in milk of first lactation. Orthogonal contrasts were used to evaluate the effect of the parity of the dam (Prim-NoL vs. Mult-NoCD + Mult-CD) and the effect of clinical disease occurrence in the previous lactation among multiparous dams (Mult-NoCD vs. Mult-CD). Compared with daughters of multiparous cows, daughters of Prim-NoL were lighter at birth (36 vs. 41 kg), had greater genetic merit for production traits (e.g., genomic estimated breeding value for milk yield: 875 vs. 746 kg), were less likely to leave the herd (17 vs. 28%) and to lose pregnancy as a heifer (9 vs. 14%), calved earlier (703 vs. 711 d old), were less likely to have clinical diseases as a first lactation cow (30 vs. 37%), and had reduced performance in the first lactation when considering their genetic merit (e.g., 305-d yield of energy-corrected milk: 11,270 vs. 11,539 kg). Compared with daughters of Mult-NoCD, daughters of Mult-CD were less likely to have digestive problems as a heifer (17 vs. 27%) and clinical disease as a first lactation cow (32 vs. 42%), but were also more likely to leave the herd as a heifer (32 vs. 25%) even though genetic merit for production traits were similar (e.g., genomic estimated breeding value for milk: 744 vs. 749 kg). In conclusion, both parity and health status of the dam in the previous lactation were associated with morbidity, survival, and performance of their daughters from birth through 305 d in milk of the first lactation and might represent factors affecting developmental programming of dairy heifers in utero.

Key words: developmental programming, health, performance, survival

INTRODUCTION

The field of research named "developmental origins of health and disease" (**DOHaD**) studies how environmental and maternal factors (e.g., stressor, nutrition, metabolism) alter conceptus development and programming in utero that could result in short- and long-term consequences to postnatal offspring health (Fleming et al., 2015). This area of research started with the Barker hypothesis in the early 1990s, and has since received increasing attention from the medical community, becoming one of the major areas of research in biomedical sciences (Barker, 2007). Over the years, supporting evidences for the DOHaD theory have been accumulated and, gradually, its concepts are influencing public health policies around the world (Barker et al., 2013; Stephenson et al., 2018). It is noteworthy that not only the gestation period, but also the preconception period, have been perceived as critical for pregnancy outcomes and postnatal health of offspring (Stephenson et al., 2018).

In addition to its importance in biomedical sciences, the main concepts of DOHaD seem to be also relevant for livestock, not only to animal health but also to production performance. For instance, there is growing evi-

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dence that environmental and maternal characteristics during gestation can influence health, reproduction, and production traits in ruminants (Berry et al., 2008; Opsomer et al., 2016; Chavatte-Palmer et al., 2018; Vonnahme et al., 2018). Nonetheless, multiple research models used to study DOHaD in livestock animals were developed as proof of concept, and not necessarily reflect conditions commonly observed in commercial herds. Thus, more epidemiological studies in large populations are required to establish the importance of prenatal programming in livestock production. Moreover, reliable genetic predictions for production traits are now possible using genomic testing, which could be a useful tool to identify and explain nongenetic variation of important traits and their phenotypic plasticity.

Lactation per se and health status during lactation are 2 major factors that cause changes in oocyte quality and uterine environment and affect reproductive success in dairy cows (Chagas et al., 2007; Leroy et al., 2008; Bromfield et al., 2015; Ribeiro et al., 2016). Lactating cows are generally less fertile than nulliparous heifers, and this association has been considered a consequence of the remarkable nutritional demands imposed by lactation in the modern dairy cow compared with the nutritional demands of a growing heifer (Chagas et al., 2007; Leroy et al., 2008; Santos et al., 2010). Comparisons between heifers and lactating cows or between lactating and nonlactating cows have showed important differences in overall metabolism and in the biology of the ovaries, the uterus, and pregnancy (Sartori et al., 2004; Wiltbank et al., 2006; Cerri et al., 2012; Maillo et al., 2012; Valour et al., 2014). In addition, a large proportion of lactating cows experience postpartum clinical diseases (i.e., metritis, mastitis, lameness, and digestive and respiratory problems), which have long-term consequences on reproduction (Ribeiro and Carvalho, 2017; Carvalho et al., 2019). Similar to lactation, clinical diseases have consequences for the metabolism of the cow and the biology of ovaries, uterus, and pregnancy, increasing the incidence of reproductive failures (Bromfield et al., 2015; Ribeiro et al., 2013, 2016). Nonetheless, it is still unknown whether lactation and clinical diseases cause any alterations in developmental programming in pregnancies that survive to term.

Therefore, our objectives were to investigate whether the effects of parity and clinical diseases on reproductive biology of dairy cows extend into the postnatal life in pregnancies that survive to term. We hypothesized that dams that had clinical disease during the lactation in which the pregnancy was established would have a suboptimal uterine environment that could influence conceptus development and programming, leading to poorer postnatal health and performance of their offspring. We also hypothesized that heifers born from primiparous cows, thus nonlactating heifers during pregnancy, would have better health and performance when compared with daughters of multiparous cows, as a consequence of enhanced uterine environment and conceptus programming.

MATERIALS AND METHODS

Animals, Housing, and General Management

This study involved a retrospective analysis of data of 1,811 Holstein heifers derived from AI and born from December 2012 to March 2014 in a large dairy operation located in Florida, which were followed from birth through 305 DIM of first lactation. Heifers were born in maternity pens with sand bedding, separated from their dam, weighed using a conventional scale, and fed 4 L of colostrum with >70 g/L of IgG during the first 6 h of life. Heifers were then housed in individual elevated pens of approximately 2 m^2 placed in an open-side barn. Preweaned heifers received 6 L of pasteurized milk per day and had ad libitum access to water and concentrate feed. Weaning was performed on wk 8 after birth, initially reducing milk feeding to 3 L/d for 3 d and then removing it completely. After weaning, heifers were housed in dry-lot pens in groups of 50 to 100 heifers. Heifers were fed a TMR to meet the nutrient requirements of growing Holstein heifers gaining 0.9 kg of BW/d based on NRC (2001) recommendations. Three weeks before the expected calving date, pregnant heifers were moved to a maternity freestall barn, which was open-side and equipped with fans, sprinklers, and stalls with sand bedding. At the time of calving, heifers were moved into maternity pens with sand bedding. After calving, primiparous cows were housed separately from herd's multiparous cows in freestall barns equipped with tunnel ventilation and stalls with sand bedding. Feed was delivered twice a day as a TMR, formulated to meet the nutrient requirements of lactating cows producing 40 kg/d of milk according to the NRC (2001). Cows were milked 3×/d and yields of milk were recorded at each milking (SmartDairy meter, Boumatic, Madison, WI). Official milk tests of the DHIA were performed monthly. Cows were managed according to standard operating proceedings, and all management procedures were performed by trained personnel and supervised by the herd veterinarians and the Food Animal Reproduction and Medicine Service of the Veterinary College at the University of Florida.

Experimental Design

Heifers were categorized into 3 groups according to parity and health status of their dams: (1) daughters

of primiparous cows that, consequently, were nonlactating heifers during gestation (**Prim-NoL**; n = 787); (2) daughters of multiparous cows that did not have any clinical diseases in the previous lactation (**Mult-NoCD**; n = 638); and (3) daughters of multiparous cows that had at least one clinical disease in the previous lactation (**Mult-CD**; n = 386). Clinical diseases of the multiparous dams included retained placenta, metritis, mastitis, lameness, and digestive and respiratory problems. Information regarding heifer's birth characteristics, morbidity, reproduction, culling, and milk production in the first lactation were collected. All data of dams and heifers were stored and retrieved from farm management software PCDart (DRMS, Raleigh, NC). In addition to pairwise comparisons among the 3 experimental groups, orthogonal contrasts were used to evaluate the effect of the parity of the dam (Prim-NoL vs. Mult-NoCD + Mult-CD) and the effect of clinical disease occurrence in the previous lactation among multiparous dams (Mult-NoCD vs. Mult-CD).

Clinical Diseases of Multiparous Dams

Health status of all cows was monitored daily by the farm personnel, which were continuously trained and supervised by the herd veterinarians and by the Food Animal Reproduction and Medicine Service of the Veterinary College at the University of Florida. Retained placenta was defined as visible fetal membranes at the vulva 24 h after calving. Metritis was characterized by abnormal vaginal discharge observed during the first 21 DIM. Incidence of clinical mastitis was evaluated before every milking and characterized by the presence of abnormal milk or by local signs of inflammation in one or more quarters. Cows that stood and walked with arched back and had short strides in one or more legs were classified as clinically lame. Digestive problems were characterized by diarrhea, bloat, or displacement of abomasum. Respiratory problems were characterized by increased respiratory frequency associated with fever and presence of increased lung sounds at auscultation.

Vaccination Program of Dams

The vaccination program was identical for dams of all 3 groups and included the administration of 1 dose of an inactivated culture of *Leptospira canicola*, *Leptospira grippotyphosa*, *Leptospira hardjo*, *Leptospira icterohemorrhagiae*, and *Leptospira pomona* at pregnancy confirmation 2 to 3 mo after AI; 2 doses of an inactivated vaccine for rotavirus, coronavirus, enterotoxigenic strains of *Escherichia coli*, and *Clostridium perfringens* type C at 7 to 8 mo of pregnancy; 2 doses of an inactivated vaccine against *E. coli* mastitis at 7 to 8 mo of pregnancy; and 1 dose of an inactivated culture of *Clostridium chauvoei*, *Clostridium septicum*, *Clostridium novyi*, *Clostridium sordellii*, *Cl. perfringens*, and *Histophilus somni* at 8 mo of pregnancy.

Genomic Merit and Phenotypic Characteristics of Heifers at Birth

Information of gestation length, calving assistance, and BW were recorded at birth for all heifers. In addition, genomic testing information was available for 1,699 heifers (i.e., 93.8% of all heifers). The genomic EBV (**GEBV**) for yields of milk, fat, and protein were calculated as 2 times the genomic PTA, which in turn was obtained from a commercial genomic test (Clarifide, Zoetis Genetics, Kalamazoo, MI).

Morbidity and Culling of Heifers

Incidence of clinical health problems, death losses, and sales were recorded by trained farm employees. Culling was characterized by heifers that left the herd either by death or sale. Clinical health problems included digestive and respiratory problems. A digestive problem was characterized by loose or watery feces, and a respiratory problem was characterized by bilateral nasal or eye discharges, by repeated coughs, or both. Additional diseases with minor incidence were all grouped as "other" and included heifers with lameness, clinical mastitis, severe eye infections, and a few cases without a final diagnosis.

Reproduction of Heifers

Heifers were moved to breeding pens when they weighed approximately 350 kg. Reproductive management was based on visual estrous detection aided by the use of tail chalk. Prostaglandin $F_{2\alpha}$ was administered every other week in heifers that were not bred or pregnant. Both AI and embryo transfer (**ET**) were used according to the management breeding strategies and were performed by skilled technicians. After the first breeding, heifers that returned to estrus were considered nonpregnant and were rebred on the same day. Pregnancy diagnosis for heifers that did not return to estrus was performed approximately 45 d after breeding by rectal palpation and those diagnosed nonpregnant were enrolled in an Ovsynch program for rebreeding. Heifers diagnosed pregnant were rechecked 45 d later and those which were reconfirmed as pregnant were followed until parturition for confirmation of calving. All

pregnancy losses after gestational d 45 were recorded. Date and outcome of all breeding were recorded.

Morbidity and Culling in the First Lactation

Incidence of clinical diseases, death, and sales were recorded from the day of calving through 305 DIM. Disease definitions and diagnosis methods were identical to those described above for characterizing health status of multiparous dams. Culling was characterized by cows that left the herd either by death or sale from the day of calving through 305 DIM.

Reproduction in the First Lactation

The voluntary waiting period was 49 DIM. Estrus detection and synchronization of the estrous cycle were used concomitantly for breeding-eligible cows by AI or ET. After the end of the voluntary waiting period, cows were evaluated daily for signs of estrus and those observed in estrus were inseminated on the same day or received an embryo 6 to 9 d after. Cows not observed in estrus were bred after a Presynch-Ovsynch program. After the first postpartum breeding, cows that returned to estrus were considered nonpregnant and were rebred on the same day. Pregnancy diagnosis of cows that did not return to estrus was performed by rectal palpation 45 d after breeding. Cows diagnosed as nonpregnant at pregnancy diagnoses were enrolled in an Ovsynch program for rebreeding. Cows diagnosed pregnant were rechecked 45 d later and those reconfirmed pregnant were followed until termination of pregnancy, either by pregnancy loss or a subsequent calving. Date and outcome of all breeding performed through 305 DIM were recorded.

Milk Production and Milk Components in the First Lactation

Daily milk yields were summarized weekly and evaluated through wk 14 of lactation. In addition, 305-d yields of milk, fat, and protein were collected. Cows that left the herd before 100 DIM did not contribute to the 305-d yield data, and those that left the herd from 100 to 304 DIM contributed with their projected values. The projections were calculated by the DHIA tool, which considers DHIA test results and DIM of the cow on the day of testing, parity of the cow, calving season, and region of the farm. Records regarding yields of milk, fat, and protein, and fat and protein percentages collected in the first 3 official DHIA milk tests were also evaluated. Energy-corrected milk for 305-d yields and for DHIA milk tests were calculated by the following equation: ECM = [(0.327 × kg of milk) + (12.95 × kg of milk fat) + (7.20 × kg of milk protein)].

Statistical Analyses

Statistical analyses were performed in SAS version 9.3 (SAS/STAT, SAS Institute Inc., Cary, NC). Continuous variables were analyzed by ANOVA and binary variables were analyzed by logistic regression using the GLIMMIX procedure. The interval to an event was analyzed by the Cox's proportional hazard model using the PHREG procedure of SAS. Survival plots were generated with MedCalc version 12.7.2 (MedCalc Software, Mariakerke, Belgium).

The statistical models included category of the dam, birth date of the heifers categorized in seasons (1 to 4), and their interactions. Each season represented 4 mo in a row: 1 = December 2012 to March 2013; 2 = April 2013 to July 2013; 3 = August 2013 to November 2013; and 4 = December 2013 to March 2014. Analyses of breeding and calving per breeding and pregnancy losses also included the effects of breeding type (AI or ET) and its interactions with category of the dam and season of birth. Weekly averages of daily milk yield in the first 14 wk of lactation, and milk yield and milk composition in the first 3 DHIA milk tests were analyzed as repeated measures. In these analyses, week of lactation or test number, and their interactions with category of the dam and season of birth, were included as fixed effects, and cow nested within category of the dam was included as a random effect. In addition, for all milk production outcomes, 2 statistical models were used. These 2 models were identical except that one included the continuous values of GEBV for the specific production trait as a covariate in the model to adjust the dependent variable with the genetic merit of the heifer. In all models, orthogonal contrasts were used to evaluate the effect of the parity of the dam (Prim-NoL vs. Mult-NoCD + Mult-CD) and the effect of clinical disease occurrence in the previous lactation among multiparous dams (Mult-NoCD vs. Mult-CD). Statistical differences were characterized by $P \leq 0.05$.

RESULTS

Genomic Merit and Phenotypic Characteristics at Birth

The GEBV for milk, fat, and protein were similar between daughters of Mult-NoCD and daughters of Mult-CD (Table 1) and averaged 747, 26, and 34 kg, respectively. Daughters of Prim-NoL, however, had greater ($P < 0.01$) GEBV for milk, fat, and protein compared with daughters of multiparous cows (Table

Table 1. Genomic estimated breeding values (GEBV) of production traits, and gestation and calving information of dairy heifers categorized according to parity and health status of their dams[1] (adjusted mean ± SEM)

	Category according to the dam				Contrast[2]	
Item	Prim-NoL	Mult-NoCD	Mult-CD	*P*-value	C1	C2
GEBV[3] (kg)						
Milk	875.3 ± 16.8[a]	744.4 ± 19.8[b]	749.2 ± 25.1[b]	<0.01	<0.01	0.88
Fat	30.8 ± 0.5[a]	26.3 ± 0.5[b]	26.0 ± 0.6[b]	<0.01	<0.01	0.80
Protein	40.3 ± 0.6[a]	34.0 ± 0.7[b]	33.1 ± 1.0[b]	<0.01	<0.01	0.46
Gestation length (d)	274.7 ± 0.2[b]	277.3 ± 0.2[a]	277.3 ± 0.3[a]	<0.01	<0.01	0.95
Dystocia of the dam (%)	9.7 ± 1.1[b]	16.4 ± 1.6[a]	16.7 ± 2.0[a]	<0.01	<0.01	0.89
BW at birth (kg)	35.6 ± 0.17[b]	41.1 ± 0.20[a]	41.2 ± 0.26[a]	<0.01	<0.01	0.80

[a–c]Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of 1,811 heifers categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 787), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 638), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 386). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems. Information regarding gestation length and dystocia was available for all heifers. Genomic information was available for 1,699 heifers (93.8%) and birth weight information was available for 1,792 heifers (99.0%).

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

[3]Calculated as 2 times the genomic PTA, the value of which was obtained using commercial genomic testing (Clarifide, Zoetis Genetics, Kalamazoo, MI).

1). The average length of gestation, the proportion of dams with dystocia, and birth BW of heifers were all similar between Mult-NoCD and Mult-CD groups, and averaged 277 d, 16.5%, and 41.1 kg, respectively (Table 1). Nonetheless, all these outcomes were reduced ($P < 0.01$) in the Prim-NoL group compared with the other 2 groups (Table 1).

Morbidity and Culling Before First Calving

Morbidity as heifer was similar between all 3 groups and averaged 65.8% (Table 2). Regarding individual clinical health problems, daughters of Mult-CD had fewer ($P < 0.01$) cases of diarrhea compared with the other 2 groups (Table 2). In addition, daughters of Prim-NoL had fewer ($P = 0.03$) cases of minor incidence diseases classified as "other" compared with daughters of multiparous cows (Table 2). Incidence of pneumonia was similar between groups and averaged 53.7% (Table 2). Moreover, fewer ($P < 0.02$) Mult-CD heifers had multiple health problems compared with the other 2 groups.

When data were analyzed according to week of life, incidence of first clinical disease was smaller ($P = 0.03$)

Table 2. Clinical health problems and culling from birth through first calving in dairy heifers categorized according to parity and health status of their dams[1] (adjusted mean ± SEM)

	Category according to the dam				Contrast[2]	
Item	Prim-NoL	Mult-NoCD	Mult-CD	*P*-value	C1	C2
Digestive problem (%)	24.3 ± 1.6[a]	26.6 ± 1.8[a]	17.6 ± 2.2[b]	0.01	0.25	<0.01
Respiratory problem (%)	52.5 ± 1.9	53.6 ± 2.3	51.2 ± 2.8	0.82	0.98	0.52
Other health problem[3] (%)	2.6 ± 0.6[b]	4.2 ± 0.8[ab]	4.7 ± 1.1[a]	0.08	0.03	0.70
Morbidity (%)	66.6 ± 1.8	67.8 ± 2.2	62.5 ± 2.7	0.29	0.58	0.13
Multiple health problems (%)	20.0 ± 1.7[b]	26.6 ± 2.1[a]	16.5 ± 2.5[b]	<0.01	0.66	<0.01
Mortality (%)	7.2 ± 1.0[b]	10.8 ± 1.5[a]	11.6 ± 1.8[a]	0.04	0.01	0.72
Sold (%)	9.5 ± 1.1[c]	13.8 ± 1.6[b]	19.8 ± 2.2[a]	<0.01	<0.01	0.02
Left the herd (%)	17.2 ± 1.4[c]	25.3 ± 2.0[b]	32.0 ± 2.6[a]	<0.01	<0.01	0.04

[a–c]Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of 1,811 heifers categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 787), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 638), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 386). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems.

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

[3]Diseases with minor incidence were all grouped as "other" and included heifers with lameness, clinical mastitis, severe eye infections, and clinical cases without a final diagnosis.

in wk 2, and cumulative incidence of clinical disease was smaller ($P < 0.05$) in wk 2 to 5 in daughters of Mult-CD compared with the other 2 groups (Figure 1). The rate of morbidity during the entire period, however, was not different between groups (Table 3). Nonetheless, of all clinical cases, 97% occurred during the first 120 d of life. Within this period, the rate of digestive problem was not different between daughters of Prim-NoL and daughters of multiparous cows, but it was 30% less for daughters of Mult-CD compared with daughters of Mult-NoCD [adjusted hazard ratio: 0.70; CI (0.53–0.92); $P = 0.01$; Figure 2A]. The rate of respiratory problems ($P = 0.55$) and the rate of clinical problems in general ($P = 0.24$) during the first 120 d of age was not different between groups (Figure 2B and 2C).

Mortality of heifers was similar between Mult-NoCD and Mult-CD groups (Table 2). Nonetheless, daughters of Prim-NoL were less likely ($P = 0.01$) to die as heifer than daughters of multiparous cows (Table 2). In addition, the rate of mortality was less for daughters of Prim-NoL cows compared with daughters of multiparous cows (Table 3; Figure 3A). The proportion of heifers sold was different ($P < 0.01$) between the 3 groups, and was greater in Mult-CD followed by Mult-NoCD and then by Prim-NoL (Table 2). The rate of sales was also different ($P < 0.04$) between the 3 groups and, similar to the overall proportions, was greater in Mult-CD followed by Mult-NoCD and then by Prim-NoL (Table 3; Figure 3B). Similarly, the proportion of heifers that left the herd was different ($P < 0.03$) between the 3 groups and was greater in Mult-CD, intermediate in Mult-NoCD, and smaller in Prim-NoL (Table 2). The rate of culling was less for daughters of Prim-NoL cows compared with daughters of multiparous cows (Table 3; Figure 3C).

Reproduction of Heifers

The proportion of heifers that reached the breeding period and was bred at least once was greater in Prim-NoL compared with Mult-NoCD and Mult-CD, and did not differ between the last 2 groups (Table 4). The rate of breeding, however, was similar between groups (Table 5). Age at first breeding and age at first pregnancy were similar between the 3 groups, and averaged 396 and 427 d, respectively (Table 4). Nonetheless, daughters of Prim-NoL established a successful pregnancy and calved for the first time younger ($P < 0.03$) than daughters of multiparous cows (Table 4). The gestation length of heifers that calved was not different between groups and averaged 271 d (Table 4).

In the first breeding, pregnancy per breeding did not differ between groups, but calving per breeding was reduced ($P = 0.03$) in Mult-CD heifers compared with Prim-NoL because pregnancy losses after gestational d 45 were greater ($P = 0.02$) in Mult-CD heifers compared with Prim-NoL (Table 4). When all breedings were considered, the proportion of heifers diagnosed pregnant on d 45 and the proportion of heifers calving did not differ between groups (Table 4). However, daughters of Prim-NoL were less likely ($P < 0.01$) to lose pregnancy after d 45 than daughters of multiparous cows (Table 4). Pregnancy rate, based on pregnancy diagnosis on d 45, did not differ between groups (Table 5). Nevertheless, when only pregnancies that successfully resulted in a subsequent calving were considered, then the rate of successful pregnancy was greater ($P < 0.01$) in daughters of Prim-NoL compared with daughters of multiparous cows (Table 5). No differences in reproductive parameters were observed between Mult-NoCD and Mult-CD heifers.

Morbidity and Culling in the First Lactation

Incidence of clinical diseases in the first lactation, from calving through 305 DIM, was different ($P = 0.02$) between groups and was less for daughters of Prim-NoL compared with daughters of multiparous cows (Table 6). In addition, a smaller proportion ($P = 0.02$) of daughters of Mult-CD had clinical diseases in the first lactation compared with daughters of Mult-NoCD (Table 6). Similar to the overall incidences of clinical disease, the rate of morbidity was also less ($P = 0.01$) for daughters of Prim-NoL compared with daughters of multiparous cows, and less ($P < 0.01$) for daughters of Mult-CD compared with daughters of Mult-NoCD (Table 7; Figure 4A). When only nonuterine diseases were considered, the rate of morbidity was also greater in daughters of Mult-NoCD compared with the other 2 groups (Tables 6 and 7; Figure 4B). Incidence of uterine disease during the first 3 wk of lactation was greater ($P = 0.04$) in daughters of Mult-NoCD compared with daughters of Prim-NoL, and both groups did not differ from the Mult-CD group (Table 6). The proportion of cows that died, were sold, or culled during the first lactation did not differ between groups (Table 6). Similarly, the rate of death, sales, and culling during the first lactation did not differ between groups (Table 7).

Reproduction as First-Lactation Cows

The proportion of first-lactation cows bred at least once and the outcomes of the first postpartum breeding did not differ between groups (Table 8). When all breedings of the first lactation were considered, the proportion of cows diagnosed pregnant did not differ between groups, but the proportion of cows that had

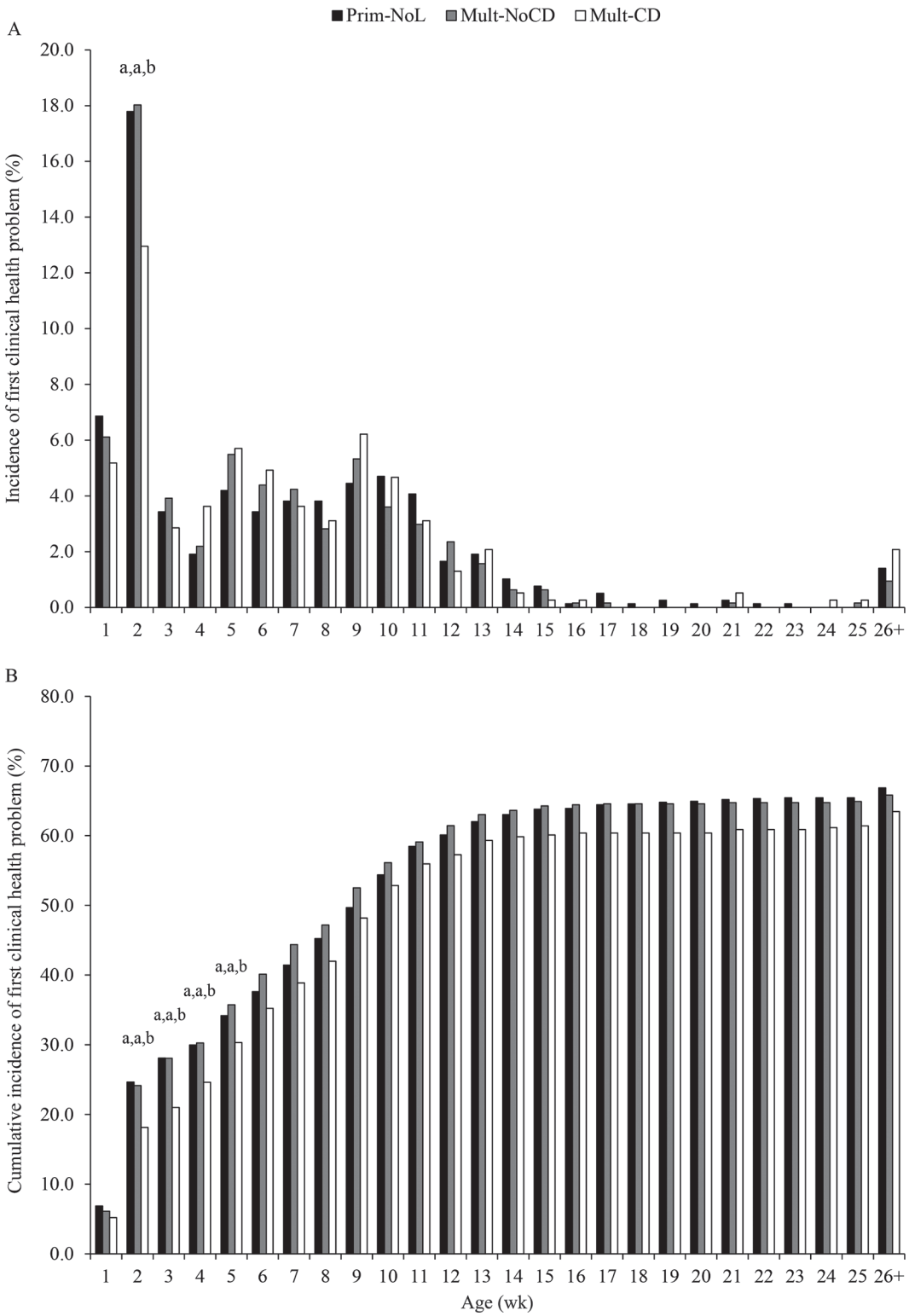

Figure 1. Incidence (A) and cumulative incidence (B) of first clinical health problem in dairy heifers categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 787), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 638), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 386). Within week, different letters (a,b) represent statistical differences between the respective sequence of bars ($P < 0.05$).

Table 3. Rate of morbidity and culling from birth through first calving in dairy heifers categorized according to parity and health status of their dams[1] (adjusted hazard ratio, with 95% CI in parentheses)

	Category according to the dam				Contrast[2]	
Item	Prim-NoL	Mult-NoCD	Mult-CD	*P*-value	C1	C2
Morbidity[3]	1.00 (0.88–1.14)	1.0 (referent)	0.90 (0.77–1.06)	0.36	0.38	0.21
Mortality	0.62 (0.44–0.86)[b]	1.0 (referent)[a]	0.99 (0.68–1.42)[a]	<0.01	<0.01	0.94
Sales	0.56 (0.41–0.76)[c]	1.0 (referent)[b]	1.40 (1.03–1.89)[a]	<0.01	<0.01	0.03
Culling[4]	0.58 (0.47–0.73)[b]	1.0 (referent)[a]	1.21 (0.96–1.52)[a]	<0.01	<0.01	0.11

[a–c]Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of 1,811 heifers categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 787), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 638), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 386). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems.

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

[3]Interval to first clinical health problem.

[4]Interval to leaving the herd, including deaths and sales.

a second calving was greater ($P = 0.04$) for daughters of Prim-NoL compared with daughters of multiparous cows (Table 8).

Milk Production in the First Lactation

The first 3 official milk tests were performed at similar intervals in the 3 groups, averaging 31.3 ± 0.3, 61.7 ± 0.3, and 91.8 ± 0.3 DIM. When GEBV were not included in the statistical models, yields of fat were less ($P = 0.02$) for daughters of Prim-NoL compared with daughters of multiparous cows (Prim-NoL = 1.31 vs. Multiparous = 1.34 kg), and yields of milk, protein, and ECM did not differ between groups (Table 9). When GEBV were included in the statistical models as a covariate, yields of fat (Prim-NoL = 1.31 vs. multiparous = 1.35 kg) and ECM (Prim-NoL = 37.6 vs. multiparous = 38.5 kg) in the first 3 milk tests were reduced in daughters of Prim-NoL compared with daughters of multiparous cows (Table 9). In general, yields of milk and protein in the first 3 tests did not differ between groups, but in the second test specifically, yields of milk and protein were smaller ($P < 0.05$) for Prim-NoL compared with Mult-NoCD when GEBV were included in the statistical models (Table 9). No differences between Mult-NoCD and Mult-CD groups were observed (Table 9).

Regarding 305-d yields of milk, fat, protein, and ECM, when GEBV were not included in the statistical models, no differences were observed between groups except for fat yield, which was smaller for daughters of Prim-NoL compared with daughters of multiparous cows (Table 10). When GEBV were included in the statistical models as a covariate, 305-d yields of milk (Prim-NoL = 11,227 vs. multiparous = 11,380 kg), fat (Prim-NoL = 398 vs. Multiparous = 409 kg) and ECM (Prim-NoL = 11,270 vs. multiparous = 11,539 kg) were all reduced ($P < 0.05$) in daughters of Prim-NoL compared with daughters of multiparous cows (Table 10). No differences were observed between Mult-NoCD and Mult-CD groups.

Similarly, the weekly averages of daily milk yield for the first 14 wk of lactation were similar between groups when GEBV were not included in the statistical models, but were smaller ($P = 0.04$) in daughters of Prim-NoL compared with daughters of multiparous cows when GEBV were considered (PrimNoL = 36.5 vs. Multiparous = 37.0 kg; Figure 5). Within week, milk yield was different between daughters of Prim-NoL and daughters of multiparous in wk 1 and from wk 5 to 14 (Figure 5).

DISCUSSION

Inflammatory clinical diseases caused by microbial infection and tissue injury, such as metritis, mastitis, lameness, displaced abomasum, and pneumonia, are prevalent in postpartum dairy cows and have a negative effect on reproductive efficiency of dairy herds (Santos et al., 2010; Ribeiro et al., 2013, 2016). Approximately 50% of dairy cows have at least one clinical disease by 305 DIM, and the odds of pregnancy per breeding and calving per breeding in these cows are reduced substantially because of failures in fertilization and postfertilization survival of the developing pregnancy (Ribeiro et al., 2016; Carvalho et al., 2019). Most cases of clinical diseases occur in the first 3 wk of lactation, thus weeks before the first postpartum breeding. Even though the vast majority of cows are clinically healthy at time of breeding and throughout gestation, health

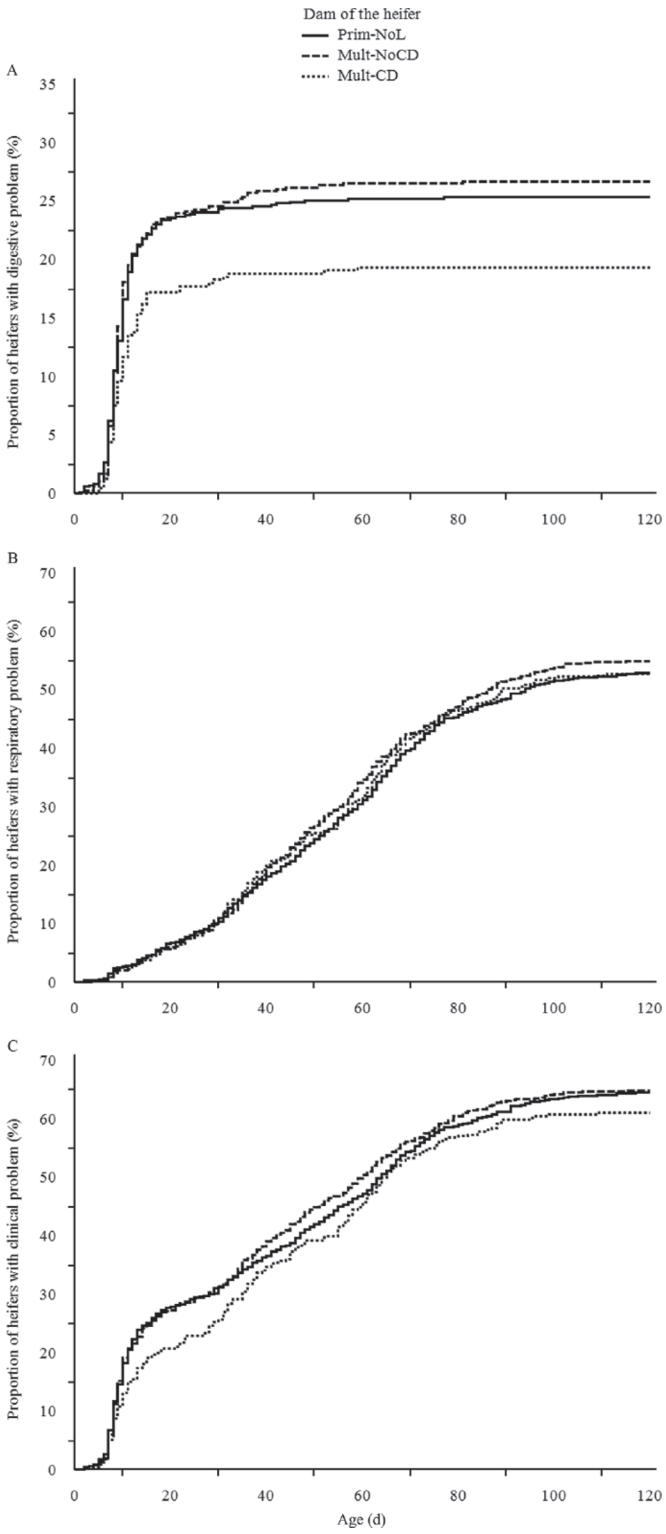

Figure 2. Probabilities of digestive (A), respiratory (B), and clinical (C) health problems in the first 120 d of life of dairy heifers categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 787), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 638), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 386).

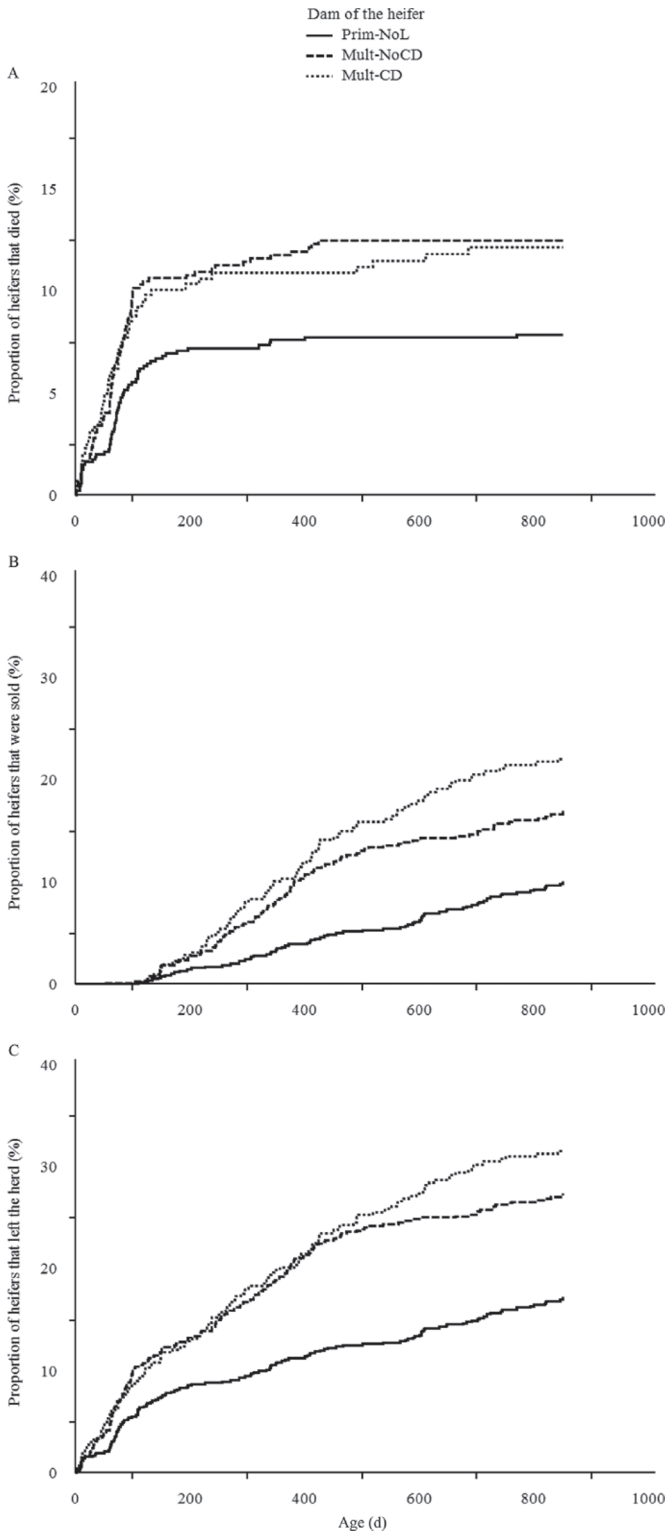

Figure 3. Probabilities of mortality (A), sale (B), and culling (C) of dairy heifers categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 787), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 638), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 386).

Table 4. Reproductive outcomes in dairy heifers categorized according to parity and health status of their dams[1] (adjusted mean ± SEM)

Item	Category according to the dam			*P*-value	Contrast[2]	
	Prim-NoL	Mult-NoCD	Mult-CD		C1	C2
Bred at least once (%)	88.8 ± 1.2[a]	82.0 ± 2.0[b]	81.6 ± 2.7[b]	<0.01	<0.01	0.90
Age at first breeding (d)	396.1 ± 0.6	396.2 ± 0.7	396.1 ± 1.0	0.99	0.96	0.97
Age at first pregnancy (d)	426.1 ± 1.8	428.8 ± 2.3	427.7 ± 3.0	0.64	0.41	0.76
Age at successful pregnancy[3] (d)	432.2 ± 2.2[b]	440.6 ± 2.7[a]	439.7 ± 3.7[ab]	0.03	0.01	0.84
Age at first calving (d)	703.2 ± 2.2[b]	710.9 ± 2.8[a]	710.4 ± 3.9[ab]	0.06	0.02	0.91
Gestation length (d)	270.9 ± 0.3	270.4 ± 0.4	270.7 ± 0.5	0.48	0.37	0.55
Outcomes of first breeding						
Pregnant d 45 (%)	50.8 ± 2.1	50.0 ± 3.0	44.5 ± 4.0	0.37	0.27	0.27
Calving (%)	44.0 ± 2.1[a]	42.4 ± 3.0[ab]	34.1 ± 3.8[b]	0.08	0.07	0.09
Pregnancy loss after d 45 (%)	10.4 ± 2.2[b]	11.6 ± 3.2[ab]	21.6 ± 5.0[a]	0.06	0.11	0.08
Outcomes for all breeding combined						
Pregnant d 45 (%)	98.8 ± 0.4	97.6 ± 8.8	97.0 ± 0.8	0.99	0.97	0.99
Calving (%)	95.2 ± 0.8	93.3 ± 1.2	93.7 ± 1.9	0.41	0.23	0.87
Pregnancy loss after d 45 (%)	9.3 ± 1.2[b]	13.7 ± 1.8[a]	15.2 ± 2.4[a]	0.03	<0.01	0.61

[a,b]Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of 1,811 heifers categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 787), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 638), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 386). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems.

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

[3]Successful pregnancies were considered those that resulted in a new calving. The day of successful pregnancy was considered the day of breeding that resulted in pregnancy that survived to term.

problems that occur in the early postpartum period seem to have enduring consequences for ovaries and uterus that ultimately impair conceptus development and survival (Bromfield et al., 2015; Ribeiro et al., 2016; Carvalho et al., 2019).

Despite the reproductive inefficiency of cows that have clinical diseases, a large proportion of calves are born from cows that had clinical diseases during the preconception and gestation periods. In this study, we investigated whether the reported effects of clinical diseases on reproductive biology would be extended to the postnatal life of pregnancies that survive to term, influencing health and performance of the offspring. Interestingly, daughters of cows that had clinical diseases in the lactation when the pregnancy was generated had reduced incidence of clinical diseases as a young heifer and as a first-lactation cow, indicating that the health status of the dam could affect the disease susceptibil-

Table 5. Rate of breeding and pregnancy in dairy heifers categorized according to parity and health status of their dams[1] (adjusted hazard ratio with 95% CI in parentheses)

Item	Category according to the dam			*P*-value	Contrast[2]	
	Prim-NoL	Mult-NoCD	Mult-CD		C1	C2
Breeding	1.01 (0.90–1.13)	1.0 (referent)	0.96 (0.83–1.11)	0.77	0.61	0.55
Pregnancy[3]	1.09 (0.97–1.23)	1.0 (referent)	1.04 (0.89–1.20)	0.36	0.21	0.64
Successful pregnancy[4]	1.17 (1.04–1.32)[a]	1.0 (referent)[b]	1.00 (0.86–1.16)[b]	0.02	<0.01	0.97

[a,b]Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of 1,504 heifers that were moved to breeding pens and had the opportunity to be inseminated. They were categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 698), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 503), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 303). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems.

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

[3]Interval to pregnancy. The day of pregnancy was considered the day of the first breeding that resulted in positive pregnancy diagnosis 45 d after breeding.

[4]Interval to pregnancy that resulted in a new calving. The day of successful pregnancy was considered the day of breeding that resulted in pregnancy that survived to term.

Table 6. Clinical diseases and culling through 305 DIM in first-lactation cows categorized according to parity and health status of their dams[1] (adjusted mean ± SEM)

Item	Category according to the dam			*P*-value	Contrast[2]	
	Prim-NoL	Mult-NoCD	Mult-CD		C1	C2
Incidence of clinical disease[3] (%)						
All diseases	30.1 ± 1.9[b]	41.9 ± 2.6[a]	31.8 ± 3.2[b]	<0.01	0.02	0.02
Nonuterine only	18.2 ± 1.6[b]	23.6 ± 2.2[a]	17.6 ± 2.6[ab]	0.08	0.35	0.09
Uterine only	15.3 ± 1.5[b]	22.6 ± 2.2[a]	16.7 ± 2.6[ab]	0.01	0.07	0.09
Dead (%)	2.2 ± 0.7[b]	5.2 ± 1.1[a]	3.1 ± 1.1[ab]	0.07	0.12	0.23
Sold (%)	9.6 ± 1.2	9.4 ± 1.6	13.3 ± 2.3	0.27	0.38	0.16
Left the herd (%)	12.5 ± 1.3	15.4 ± 1.8	16.4 ± 2.5	0.24	0.09	0.78

[a,b]Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of 1,367 first-lactation cows categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 684), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 458), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 261). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems.

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

[3]Uterine diseases included retained placenta and metritis in the first 21 d postpartum, and nonuterine disease included clinical mastitis, lameness, and digestive and respiratory problems from calving through 305 DIM.

ity of the offspring. According to the DoHaD theory, prenatal programming might represent evolutionary strategies to improve the chances of survival in a hostile environment, also known as a predictive adaptive response (Gluckman et al., 2005). Thus, the altered uterine environment of cows that had clinical diseases might induce adaptive changes in the conceptus that could improve its resilience or tolerance to postnatal health challenges and consequently improve chances of survival.

The mechanism by which clinical diseases could induce a predictive adaptive response, however, is unknown. Heifers born from cows that had disease and those born from cows that did not have disease were similar in size at birth, and had similar milk production in the first lactation, which are 2 important factors associated with susceptibility to diseases. Nevertheless, prenatal programming of the immune system could be a possible explanation. Williams et al. (2011) performed an immunological challenge with LPS in female mice shortly after breeding to induce inflammation when the zygotes were being generated, and then compared those with a control group that was not challenged. The same LPS challenge was performed in the offspring of challenged and not challenged dams, and the inflammatory response was reduced in mice whose dams were challenged at the time of conception. In addition, the LPS challenge of the dam caused a reduction in the

Table 7. Rate of morbidity and culling through 305 DIM in first-lactation cows categorized according to parity and health status of their dams[1] (adjusted hazard ratio with 95% CI in parentheses)

Item	Category according to the dam			*P*-value	Contrast[2]	
	Prim-NoL	Mult-NoCD	Mult-CD		C1	C2
Morbidity[3]						
All clinical diseases	0.65 (0.53–0.79)[b]	1.0 (referent)[a]	0.69 (0.53–0.89)[b]	<0.01	0.01	<0.01
Nonuterine diseases only	0.71 (0.55–0.92)[b]	1.0 (referent)[a]	0.67 (0.48–0.94)[b]	0.01	0.26	0.02
Mortality	0.56 (0.31–1.03)	1.0 (referent)	0.59 (0.27–1.32)	0.14	0.31	0.20
Sales	0.89 (0.61–1.29)	1.0 (referent)	1.23 (0.79–1.90)	0.32	0.19	0.36
Culling[4]	0.78 (0.57–1.07)	1.0 (referent)	1.02 (0.70–1.49)	0.22	0.08	0.92

[a,b]Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of 1,367 first-lactation cows categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 648), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 458), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 261). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems.

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

[3]Interval to first clinical health problem, including retained placenta, metritis, mastitis, lameness, and digestive and respiratory problems.

[4]Interval to leaving the herd, including mortality and sales.

blastocyst inner cell mass, as well as the ratio of inner cell mass to trophectoderm cells (Williams et al., 2011). Thus, inflammatory responses of the dam might affect not only the development of the conceptus in utero but might also result in postnatal adaptations in pregnancies that survive to term. Interestingly, preimplantation conceptus recovered from cows that had disease before AI presented upregulation of genes associated with inflammatory response, and inflammatory molecules such as LPS, tumor necrosis factor α, and IFN-γ were predicted as potential upstream regulators of such differences.

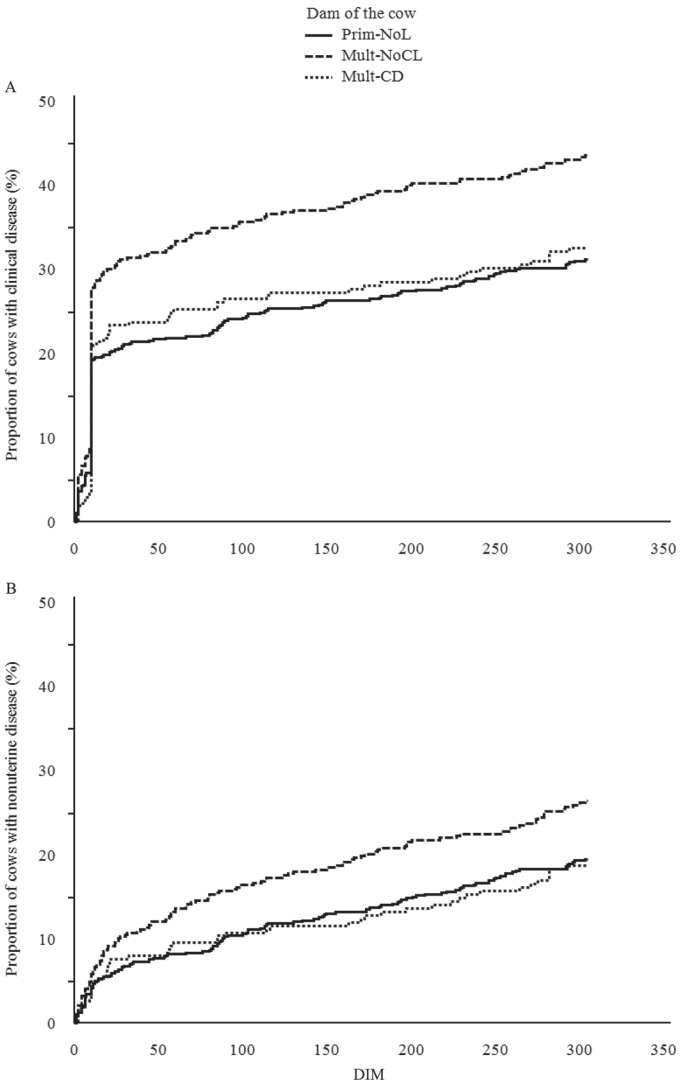

Figure 4. Probabilities of clinical disease (A) and nonuterine clinical disease (B) morbidity of first-lactation cows (n = 1,367) categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 648), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 458), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 261). Clinical diseases included retained placenta, metritis, mastitis, lameness, and digestive and respiratory problems. Nonuterine clinical diseases included mastitis, lameness, and digestive and respiratory problems.

Despite reduced incidence of clinical diseases and similar genetic merit for milk production, heifers born from cows that had clinical disease in the previous lactation were more likely to leave the herd than those born from cows that did not have clinical disease. This difference in culling rates was mainly explained by sales of heifers. Unfortunately, we do not have sufficient information regarding culling decisions to explain these differences. Nevertheless, it is noteworthy that this commercial herd prioritizes culling of less desirable heifers based on their genetics and conformation and, therefore, additional differences between the 2 groups of heifers could exist and were not captured in our study. Postweaning differences in body growth and conformation were not evaluated in our study and might deserve greater attention in future studies. Similar to our findings, González-Recio et al. (2012) reported that daughters of cows that had subclinical mastitis during gestation had a shorter productive lifespan.

Years of genetic selection for milk production have intensified the homeorhetic control of dairy cow metabolism to support lactation (Bauman and Currie, 1980). In fact, the modern high-producing dairy cow has remarkable nutrient demands, with total requirements averaging 4 times the maintenance requirements (Chagas et al., 2007; Santos et al., 2010). As a consequence, metabolism and endocrinology are drastically different between lactating and nonlactating cows or between lactating cows and nonlactating heifers, and include differences in circulating levels of glucose, insulin, IGF-1, nonesterified fatty acids, and steroid hormones, which affect the biology of reproductive tissues (Sartori et al., 2004; Wiltbank et al., 2006; Cerri et al., 2012; Maillo et al., 2012; Valour et al., 2014). Although the concept that lactation requirements cause changes in conceptus development and survival in utero is widely accepted, limited information is available regarding its potential effect on developmental programming of the offspring (Swali and Wathes, 2007; Berry et al., 2008; Opsomer et al., 2016).

In our study, we compared daughters of primiparous cows and daughters of multiparous cows. In the former group, gestation occurred when their dams were still growing heifers, whereas in the latter group, at least 7 mo of gestation occurred when cows were lactating. In addition to lactation, the comparison also included differences in environment, management, diet, and age of the dams. But considering that all daughters were managed equally and in the same environment, the comparison is still relevant to understand how major

Table 8. Reproductive outcomes in first-lactation cows categorized according to parity and health status of their dams[1] (adjusted mean ± SEM)

Item	Category according to the dam			*P*-value	Contrast[2]	
	Prim-NoL	Mult-NoCD	Mult-CD		C1	C2
Bred at least once (%)	92.9 ± 1.0	91.3 ± 1.4	89.2 ± 2.1	0.21	0.10	0.39
Outcomes of first postpartum breeding						
Pregnant d 45 (%)	37.5 ± 2.4	36.8 ± 2.6	39.6 ± 3.8	0.70	0.95	0.40
Calving (%)	32.0 ± 2.3	28.9 ± 2.5	33.2 ± 3.7	0.52	0.75	0.32
Pregnancy loss after d 45 (%)	12.6 ± 2.9	17.4 ± 3.5	13.6 ± 4.1	0.52	0.46	0.48
Outcomes for all breeding combined						
Pregnant d 45 (%)	92.4 ± 1.1	89.8 ± 1.6	89.8 ± 2.3	0.30	0.14	0.99
Calving (%)	84.7 ± 1.5[a]	79.7 ± 2.1[b]	79.8 ± 2.9[ab]	0.10	0.04	0.99
Pregnancy loss after d 45 (%)	11.2 ± 1.9	16.5 ± 2.3	14.9 ± 3.4	0.17	0.10	0.70

[a,b]Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of 1,367 first-lactation cows categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 648), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 458), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 261). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems.

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

differences in dam biology could influence health and performance of daughters. Compared with daughters of multiparous cows, daughters of primiparous cows were smaller at birth and less likely to die, to be sold, or to leave the herd as a heifer. The difference in sales is likely explained by the fact that daughters of primiparous cows had greater GEBV for production traits and, thus, were more likely to be retained in the dairy. However, the differences in mortality are likely explained by better resilience of daughters of primiparous cows, which could be a consequence of developmental programming in utero. Similar to our findings, González-Recio et al. (2012) reported that daughters of primiparous cows had longer productive lifespan.

Daughters of primiparous cows also had better reproductive performance than daughters of multiparous cows. The former group had reduced incidence of pregnancy losses, which resulted in an earlier first calving. In addition, daughters of primiparous cows had reduced incidence of clinical diseases in the first lactation, and among those enrolled in the reproductive program, daughters of primiparous cows were more likely to calve a second time. Similar to our findings, Swali and Wathes (2007) reported that daughters of primiparous cows had better fertility than daughters of multiparous cows. It is not clear how the developmental programming in utero could improve reproduction and resilience to diseases, but based on biomedical research, differences in nutrient delivery in utero could affect tissue formation and future phenotypic plasticity of important traits (Fleming et al., 2015). In laboratory animals and humans, age of the mother was reported to be inversely associated with fitness, reproduction, and lifespan of the offspring (Bock et al., 2019), which supports our findings and indicates that the underpinning mechanism associated with the observed variations in phenotypes of daughters might be linked to the age of the dam and not necessarily to metabolism of the dam.

Despite having better postpartum health and better genetic merit for production traits, daughters of primiparous cows had similar milk production in the first lactation to that observed for daughters of multiparous cows. In fact, when we included the GEBV in the statistical models, milk production of daughters of primiparous cows were actually less than that observed for daughters of multiparous cows. Similar results were reported previously in heifers derived from ET (Siqueira et al., 2017), indicating that the uterine environment during embryonic and fetal development might be responsible for such difference in milk production of first-lactation cows. The specific reason for such phenotypic plasticity, which can be considered undesirable from a production standpoint, is unclear, but might be related to developmental programming of metabolism and nutrient partition, or mammary gland development, or simply differences in body size of daughters. Valour et al. (2014) compared preimplantation conceptuses recovered from lactating cows and nulliparous heifers, and although no morphological differences were observed, 483 transcripts were differently expressed and revealed important differences in lipid and energy metabolism. Whether those differences are sustained to later stages of gestation and whether they influence metabolic programing in utero remain unknown. Swali and Wathes (2007) reported that daughters of primiparous cows had greater weight loss and reduced concentration of IGF-1 in blood during the early postpartum period after first calving compared with daughters of multiparous

cows. In the same study, daughters of primiparous also had reduced concentration of insulin in blood between 8 and 12 wk of lactation compared with daughters of multiparous cows.

The smaller body size at birth of daughters of primiparous cows could also help to explain their suboptimal production in the first lactation, especially if differences in body size were maintained during heifer development (not evaluated in this study). Previous research has reported similar differences in body size according to parity of the dam and similar associations of BW at birth with milk production in the first lactation (Swali and Wathes, 2006, 2007; Kamal et al., 2014; Siqueira et al., 2017; Vieira-Neto et al., 2017). Swali and Wathes (2007), however, reported that differences in body size were no longer apparent by 3 mo of age. The lighter birth weight of daughters of primiparous cows is at least partially explained by the observed shorter gestation length. However, the smaller body size at birth could also be a result of distinct placentation and nutrient availability at late gestation, or even potential differences in sire selection for breeding of heifers. Most fetal growth occurs at late gestation and requires large amounts of nutrients (Bell, 1995). At late stages of gestation, heifers are still growing in size and other body tissues will compete with the preg-

Table 9. Yields of milk, fat, protein, and ECM in the first 3 official DHIA milk tests of first-lactation cows categorized according to parity and health status of their dams[1] (adjusted means ± SEM)

	Category according to the dam				Contrast[2]	
Item	Prim-NoL	Mult-NoCD	Mult-CD	*P*-value	C1	C2
Model without GEBV[3]						
Milk (kg)				0.90	0.95	0.67
First test	35.7 ± 0.2	35.5 ± 0.3	35.4 ± 0.4			
Second test	39.5 ± 0.2	39.9 ± 0.3	39.7 ± 0.4			
Third test	40.5 ± 0.2	40.6 ± 0.3	40.4 ± 0.4			
Fat (kg)				0.06	0.02	0.97
First test	1.28 ± 0.01^{b}	1.31 ± 0.01^{ab}	1.32 ± 0.02^{a}			
Second test	1.32 ± 0.01	1.35 ± 0.01	1.35 ± 0.02			
Third test	1.33 ± 0.01	1.36 ± 0.01	1.34 ± 0.02			
Protein (kg)				0.91	0.92	0.69
First test	1.07 ± 0.01	1.06 ± 0.01	1.06 ± 0.01			
Second test	1.14 ± 0.01	1.16 ± 0.01	1.15 ± 0.01			
Third test	1.18 ± 0.01	1.19 ± 0.01	1.18 ± 0.01			
ECM (kg)				0.36	0.17	0.95
First test	35.9 ± 0.2	36.2 ± 0.3	36.4 ± 0.4			
Second test	38.2 ± 0.2	38.9 ± 0.3	38.8 ± 0.4			
Third test	38.9 ± 0.2	39.3 ± 0.3	39.1 ± 0.4			
Model with GEBV[3]						
Milk (kg)				0.16	0.07	0.85
First test	35.6 ± 0.2	35.8 ± 0.3	35.8 ± 0.4			
Second test	39.3 ± 0.2^{b}	40.2 ± 0.3^{a}	40.1 ± 0.4^{ab}			
Third test	40.4 ± 0.2	41.0 ± 0.3	40.8 ± 0.4			
Fat (kg)				<0.01	<0.01	0.70
First test	1.28 ± 0.01^{b}	1.31 ± 0.01^{a}	1.34 ± 0.02^{a}			
Second test	1.32 ± 0.01^{b}	1.36 ± 0.01^{a}	1.36 ± 0.02^{a}			
Third test	1.32 ± 0.01^{b}	1.36 ± 0.01^{a}	1.35 ± 0.02^{a}			
Protein (kg)				0.48	0.27	0.80
First test	1.06 ± 0.01	1.06 ± 0.01	1.07 ± 0.01			
Second test	1.14 ± 0.01^{b}	1.16 ± 0.01^{a}	1.15 ± 0.01^{ab}			
Third test	1.18 ± 0.01	1.19 ± 0.01	1.18 ± 0.01			
ECM (kg)				<0.01	<0.01	0.71
First test	35.9 ± 0.2^{b}	36.5 ± 0.3^{ab}	36.9 ± 0.4^{a}			
Second test	38.1 ± 0.2^{b}	39.3 ± 0.3^{a}	39.3 ± 0.4^{a}			
Third test	38.9 ± 0.2^{b}	39.7 ± 0.3^{a}	39.7 ± 0.4^{ab}			

^{a,b}Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of first-lactation cows (n = 1,304) categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 620), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 435), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 249). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems.

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

[3]For each dependent variable analyzed, 2 statistical models were applied. One included and the other did not include genomic estimated breeding value (GEBV) as a covariable in the model.

Table 10. Yields of milk, fat, protein, and ECM in first-lactation cows categorized according to parity and health status of their dams during 305 d of lactation[1] (adjusted mean ± SEM)

Item	Category according to the dam[1]			*P*-value	Contrast[2]	
	Prim-NoL	Mult-NoCD	Mult-CD		C1	C2
Model without GEBV[3]						
Milk (kg)	11,303 ± 57.9	11,328 ± 73.0	11,279 ± 101.7	0.92	0.99	0.70
Fat (kg)	399.6 ± 2.3[b]	408.3 ± 2.9[a]	407.5 ± 4.1[ab]	0.04	0.02	0.87
Protein (kg)	344.2 ± 1.5	344.6 ± 1.9	343.0 ± 2.7	0.88	0.87	0.62
ECM (kg)	11,349 ± 54.0	11,472 ± 68.0	11,434 ± 94.7	0.34	0.19	0.74
Model with GEBV[3]						
Milk (kg)	11,227 ± 52.1	11,378 ± 65.6	11,382 ± 91.1	0.13	0.05	0.97
Fat (kg)	398.0 ± 2.3[b]	408.8 ± 2.9[a]	410.4 ± 4.0[a]	<0.01	<0.01	0.74
Protein (kg)	342.9 ± 1.5	345.7 ± 1.9	345.1 ± 2.7	0.49	0.27	0.86
ECM (kg)	11,270 ± 50.9[b]	11,522 ± 63.9[a]	11,557 ± 88.9[a]	<0.01	<0.01	0.75

[a,b]Within a row, means with different superscripts differ ($P \leq 0.05$).

[1]Analyses include information of first-lactation cows (n = 1,272) categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 608), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 425), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 239). Clinical disease of multiparous dams included uterine diseases, mastitis, lameness, and digestive and respiratory problems. Actual 305-d yields were used for cows that stayed for 305 d in the herd, and projected yields were used for cows whose lactation lasted from 100 to 304 d. Cows whose lactation was shorter than 100 d were not included in the analyses of 305-d yields.

[2]Orthogonal contrasts: C1 = effect of parity (Prim-NoL vs. Mult-NoCD + Mult-CD); C2 = effect of disease in the previous lactation (Mult-NoCD vs. Mult-CD).

[3]For each dependent variable analyzed, 2 statistical models were applied. One included and the other did not include genomic estimated breeding value (GEBV) as a covariable in the model.

nant uterus for nutrients. On the other hand, parous cows are normally dried off at late gestation and there is little competition for nutrients with the mammary gland. Thus, protein and energy densities in the diet of pregnant heifers at late gestation should be adjusted to provide adequate level of nutrients and energy for proper fetal and mother growth.

Although not evaluated in our study, it is important to mention that epigenetic changes are often associated with developmental programming. Environmental factors such as nutrition and stressors have already been shown to have effects on epigenetic marks in multiple tissues and were associated with distinct phenotypes of the offspring (Chavatte-Palmer et al., 2018; Skibiel et al., 2018). Differences in epigenetics result in changes of gene expression and biology of tissues, which ultimately can affect the observed phenotypes. Thus, all the associations between maternal characteristics and offspring performance discussed above could represent developmental programming of heifers potentially mediated by epigenetic changes. A better understanding of these events and their associated biological mechanisms could lead to novel management strategies in livestock and further optimization of animal health and production.

CONCLUSIONS

Our results indicate that parity and health status of dams represent factors implicated in the developmental programming in utero and postnatal plasticity of health and performance phenotypes. Compared with daughters of multiparous cows, daughters of primiparous cows were born after a shorter gestation, were lighter at birth, had greater genetic merit for production traits, were less likely to die, to be sold, and to have late pregnancy losses as a heifer, were less likely to have postpartum clinical diseases and, when genetic merit for production was considered, had reduced lactation performance as a first-lactation cow. Compared with daughters of multiparous cows that did not have clinical diseases in the previous lactation, daughters of multiparous cows that had at least one clinical disease in the previous lactation were less likely to have diarrhea as a young heifer, less likely to have postpartum clinical diseases as a first lactation cow, but were more likely to be sold and to leave the herd as a heifer, even though the genetic merit for production traits were similar.

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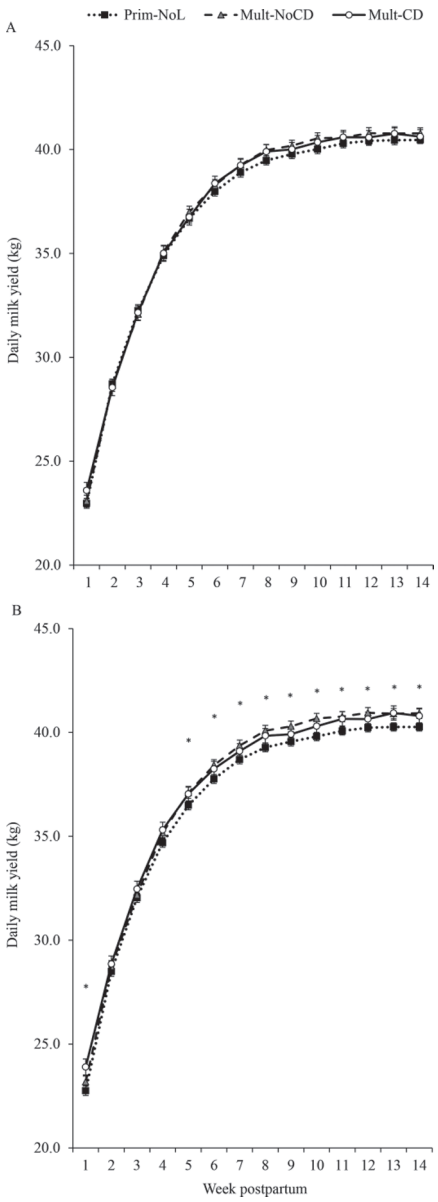

Figure 5. Average daily milk yield of first-lactation cows (n = 1,293) categorized according to parity and health status of their dams as follows: daughter of primiparous cows (Prim-NoL; n = 617), daughter of multiparous cows that did not have clinical disease in the previous lactation (Mult-NoCD; n = 431), and daughter of multiparous cows that had clinical disease in the previous lactation (Mult-CD; n = 245). Panels A and B were created with adjusted LSM and SEM for the same data but using different statistical models. The model of panel A included the fixed effects of group, time, and group by time interaction in addition to the random effect of cows nested within group. The model of panel B is identical to A but included the genomic PTA for milk production as a covariable. In panel A, the resulting probability values were as follows: group = 0.69; time <0.01; group by time interaction = 0.25; contrast of Prim-NoL versus Mult-NoCD + Mult-CD = 0.58; contrast of Mult-NoCD versus Mult-CD = 0.60. In panel B, the resulting probability values were as follows: group = 0.09; time <0.01; group by time interaction = 0.38; contrast of Prim-NoL versus Mult-NoCD + Mult-CD = 0.04; contrast of Mult-NoCD versus Mult-CD = 0.89. Within a week, statistical differences ($P < 0.05$) between daughters of Prim-NoL and daughters of multiparous cows are represented by *. Error bars represent the SEM.

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