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RESEARCH ARTICLE

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Milk yield, periparturient diseases and body condition score as factors affecting the risk of fetal losses in high-yielding Holstein cows

Miguel Mellado[1], Ulises Macías-Cruz[2], Leonel Avendaño-Reyes[2], Francisco G. Véliz[3], Leticia Gaytán[3], José E. García[1] and Alvaro F. Rodríguez[1]

[1]*Autonomous Agrarian University Antonio Narro, Dept. of Animal Nutrition, Saltillo, Mexico.* [2]*Institute of Agricultural Sciences, Autonomous University of Baja California, Mexicali, Mexico.* [3]*Autonomous Agrarian University Antonio Narro, Dept. of Veterinary Science, Torreon, Mexico.*

Abstract

The objective of this study was to assess various risk factors affecting fetal losses in high-yielding Holstein cows in a hot environment. In a retrospective observational study, 14,384 records from Holstein cows from a large highly technified dairy herd in northern Mexico were used. Logistic multivariate multiple-group response model indicated that fetal losses between 43 and 260 days of pregnancy were 23.8%. Dry periods >60 d were associated ($p<0.05$) with 0.8 (confidence interval CI=0.8–0.9) times lower incidence of fetal losses compared to cows with dry periods <60 d. Cows with body condition score (BCS) >3 at calving and 15 days postpartum had about half the risk of suffering fetal losses than cows with BCS <3.0. Cows with peak milk yield >38 kg were 5.5 times more likely to have a fetal loss than cows with peak milk yield <38 kg (36.9 *vs*. 9.6%; $p<0.01$). The risk of fetal loss increased with 305-d milk yield >9,000 kg (OR=2.1) compared with cows with milk yield <9,000 kg. Retained placenta was ($p<0.05$) associated with 1.2 (CI=1.1–1.4) times higher fetal losses than cows without this reproductive disorder. Cows suffering premature parturition had 1.2 (CI=1.0–1.4) greater ($p<0.05$) risk of suffering fetal losses than cows with normal parturition. Cows with twin pregnancies had significantly increased chances of losing their fetuses than cows with a single fetus (31.1 *vs*. 15.9 $p<0.01$). A bimodal distribution of fetal losses was observed with peaks around 50 and 220 days of pregnancy. It was concluded that in this particular hot environment fetal losses were associated with high milk yield, low body energy reserves at calving, reduced dry periods, occurrence of retained placenta, twin pregnancies and premature calving.

Additional keywords: placental retention; abortion; dry period; premature calving; twining.

Abbreviations used: AI (artificial insemination); BCS (body condition score); BRSV (bovine respiratory syncytial virus); BVD (bovine viral diarrhea); IBR (infectious bovine rhinotracheitis); OR (odds ratio); PI3 (parainfluenza-3); THI (temperature-humidity index).

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Correspondence should be addressed to Álvaro F. Rodríguez: arodriv@uaaan.mx; alvferrodriv@gmail.com

Introduction

The incidences of fetal losses in intensive dairy herds range from 7.6 to 20.5% (Starbuck *et al.*, 2004; Pontes *et al.*, 2015), a 2.7-fold difference between herds. Causes for these apparent differences are not clear, although the wide variation in the incidence of this reproductive disorder could be explained by the inconsistent definition of gestation loss among studies, the different gestational at-risk periods considered, and the wide computation methods used among studies.

Non-infectious causes of abortion play an important role in premature pregnancy conclusion. However, the infectious causes of abortion have been a primary focus of attention and the control these infectious diseases is based on several points like vaccination, but non-infectious fetal losses still is likely in dairy herds (López-Gatius & García-Ispierto, 2010). Studies that focus on fetal losses have examined factors related to genetic abnormalities (Flisikowski *et al.*, 2010) and secondary metabolites in diets offered to cows (Santos *et al.*, 2003). Other circumstances that can terminate pregnancy include heat stress (García-Ispierto *et al.*, 2006; Mellado *et al.*, 2016), high milk production (Grimard *et al.*, 2006), cow parity (Yániz *et al.*, 2010) and sub-optimal blood progesterone concentrations (López-Gatius *et al.*, 2004). Additional risk factors for early fetal losses include intensive management (López-Gatius *et al.*, 2009), parity (Labèrnia *et al.*, 1996; López-Gatius *et al.*, 2004), twin pregnancies (López-Gatius *et al.*, 2002; Silva-Del-Río *et al.*, 2009) and occurrence of mastitis (Chebel *et al.*, 2004; Pinedo *et al.*, 2009).

When managing dairy cattle, it is important to understand the factors that might be related to fetal losses because knowledge of these influences can be used to focus herd health and management practices to reduce fetal losses. Many studies on gestation losses have been carried out during the early phase of fetal development. Therefore, further elucidation of factors that cause fetal losses throughout gestation in regions with prolonged warm weather may enable the development of more effective reproductive programs in intensive dairy herds. The objectives of the present study were to evaluate various factors associated with fetal losses in high-yielding lactating Holstein cows experiencing heat stress during an extended period of the year.

Material and methods

Study design, animals, and housing

In this retrospective observational study, pregnancy data from 14,384 lactating Holstein cows from January 2011 to December 2016, from a single large dairy herd (3,300 milking cows) located in northern Mexico (25° N, 1120 m above sea level). Average annual temperature is 23.5 °C and mean temperature-humidity index (THI) = 80.0 units; range 69.8 to 85.0. The latest values derived from the equation of Mader *et al.* (2006): $THI = (0.8 \times T) + [(\%RH / 100) \times (T-14.4)] + 46.4$; where T = maximum temperature (ºC) and RH = relative humidity.

Cows were housed in open-lot, dirt floor pens with shade structures in pens. Cows were offered a total mixed ration with approximately 50% concentrate and 50% forage that were formulated to provide nutrients for maximum milk yield (NRC, 2001) for Holstein cows weighing 650 kg. Cows were fed and milked thrice daily.

Reproductive and health management

All cows were yearly vaccinated against a number of viruses causing respiratory and/or reproductive diseases such as bovine viral diarrhea (BVD), infectious bovine rhinotracheitis (IBR), bovine respiratory syncytial virus (BRSV), parainfluenza-3 (PI3) (CattleMaster Gold FP5®, Zoetis, Mexico DF, Mexico). This vaccine contains a freeze-dried preparation of chemically altered strains of IBR and PI3 viruses and modified live BRSV, noncytopathic BVD Type 1 virus strains, *Campylobacter fetus*, and five *Leptospira* serovars. Additionally, cows were vaccinated twice a year against leptospirosis using a leptospiral vaccine (LEPTAVOID-H®; Merck Sharp and Dohme Corp., Mexico, DF; inactivated *Leptospira interrogans* serovar Hardjo 204 2–3 × 10^9 organisms). Also, all cows were vaccinated against brucellosis (strain RB51; BRUCEL®, PISA laboratories, Santa Catarina, Mexico; live attenuated vaccine strains of *Brucella* abortus) at six months of age and annually thereafter. Fetal losses were registered by the herd veterinarians; spontaneous fetal loss was defined as fetal death between gestational day 43 (clinical recognition of pregnancy) and gestational day 260 (Thurmond & Picanso, 1990). Veterinarians routinely examined fresh cows few days after parturition to identify and treat cows with postpartum reproductive disorders, such as retained placenta and metritis. Artificial insemination (AI) began following a 50 d voluntary waiting period. Pregnancy diagnoses were performed by detection of either the allantochorion membrane or amniotic sac by per rectum palpation at 45 ± 3 days after the last AI. Pregnancy was reconfirmed by palpation per rectum about 50 days later.

Fetal loss was declared in cows that displayed evident visual signs of abortion (expulsion of a lifeless fetus or presence of extraembryonic membranes and vaginal discharges), return to service after being confirmed pregnant or were diagnosed open during the second pregnancy check. Per lactation, the time at risk started at pregnancy diagnosis date (43 days), and ended at 260 days of pregnancy. The abortion date was the day when unmistakable signs of abortion were observed. In the case of cows returning to service after being detected pregnant, abortion date was estimated according to uterus characteristics when palpated. When uterine horns were thick-walled and distended, an abortion date of 12 d prior to the day of palpation was used. When pregnant cows returned to estrus, the reproductive tract was examined by rectal palpation, and if the uterus was normal, the time of fetal loss was considered to have occurred 20 days prior to the day of palpation.

Study design and data management

Risks of fetal death for a current pregnancy were occurrence of previous abortion (primiparous cows not included), occurrence of mastitis (abnormalities in milk and irregularities in the udder such as swelling, heat, redness and hardness without signs of systemic illness), clinical ketosis (urine acetoacetate concentrations >80 mg/dL; Ketostix; Bayer Corp. Diagnostics Division, Elkhart, IN, USA) and retained placenta (fetal membranes retained for more than 24 h). Metritis, endometritis, and pyometra (definitions according to Sheldon *et al.*, 2006) were coded as "uterine diseases". These diseases were diagnosed and appropriately treated by the full-time herd´s veterinarians, so that they were healthy before the start of the service period.

Other probable explanatory variables associated with fetal losses investigated in this study were lactation persistence (defined as the rate of decline of milk yield between peak yield and 305 days of the lactation), body condition score (BCS) according to Ferguson *et al.* (1994) at calving and at 15 d postcalving, 305-d milk yield (recorded daily electronically on each cow with the AfiFarm Dairy Farm Management software, Kibbutz Afikim, Israel), and peak milk production. Additional factors analyzed were type of parturition (unassisted or dystocic, defined as prolonged assisted extraction), dry period length before the current lactation, premature parturition (expulsion of alive calves at approximately 276 days of pregnancy) and twin pregnancy. Is worth mentioning that definition of preterm calving in Holstein cows is divisive. When considering several thousands of parturition either in subtropical (Silva *et al.*, 1992) or temperate (Norman *et al.*, 2009) climates, gestation length of Holstein cows has been 279-280 days. However, recent data of Vieira-Neto *et al.* (2017) indicate that gestation length of Holstein cows averaged 276 days. For the present study premature parturition follow the definition of Damaso *et al.* (2018), that is, gestations <277 days.

Statistical analyses

The odds ratios (OR) for the occurrence of fetal losses during 43 to 260 days of gestation were calculated using the PROC GENMOD procedure of SAS (SAS Inst. Inc., Cary, NC, USA). Because individual pregnancies of the same cow cannot be considered independent events, the analysis was conducted taking into account the correlation of pregnancy outcomes for the same cow (REPEATED option of SAS). A preliminary full model was conducted for the following potentially explanatory variables: occurrence of abortion in previous lactations, 305-d milk yield (≤9,000 *vs.* >9,000 kg; mean ± SD for each group 8,569 ± 228, 11,104 ± 1,310, respectively), milk production at peak yield (≤38 *vs.* >38 kg; mean ± SD for each group 34.8 ± 1.5, 47.7 ± 9.5, respectively), persistency of milk production (defined as less or greater than 80%; mean ± SD for each group 71.1 ± 7.4, 82.2 ± 2.9, respectively), previous days dry (≤60 and >60 days; mean ± SD for each group 18.5 ± 24.7, 73.2 ± 31.3, respectively), calving difficulty (dichotomized variable), BCS at calving (≤3.0 *vs.* >3.0; mean ± SD for each group 2.8 ± 0.2, 3.4 ± 0.2, respectively) and at 15 d postcalving (≤2.75 *vs.* >2.75; mean ± SD for each group 2.7 ± 0.2, 3.1 ± 0.2, respectively) and occurrence of ketosis (no *vs.* clinical), mastitis (yes *vs.* no), retained placenta (yes *vs.* no), uterine diseases (yes *vs.* no), dystocia (yes *vs.* no), premature calving (yes *vs.* no), twin pregnancy and one-way interactions. The occurrence of these diseases was only considered when they did not induce termination of lactation. Non-significant independent variables and interactions were removed from the model until all remaining variables were significant. Lactation number and year were included as covariates in the final model. A histogram for the proportion of fetal losses during the gestation period studied was prepared. The Jonckheere-Terpstra test (PROC FREQ of SAS) was used to test the null hypothesis that occurrence of fetal losses is independent of days of gestation.

Results

Risk factors for the occurrence of fetal losses are indicated in Table 1. Fetal losses were 23.8% (3,426/14,384). Cows that had dry periods longer than 60 days (range 61-401 days) were less likely to lose their fetuses in the subsequent pregnancy than cows having a dry period of 60 days or less (range 0-60 days). Cows with low BCS (range 2.25-3.0) at calving presented higher fetal losses than cows with adequate BCS (range 3.25-4.0). Likewise, BCS >2.75 15 d postcalving was associated with decreased risk for fetal losses. Cows with peak milk yield >38 kg (range 39-79 kg) presented higher odds of fetal losses than cows with low peak milk yield (range 24-38 kg). In addition, cows whose 305-d milk yield was higher than 9,000 kg (range 9,000-14,623) were more likely to have a fetal loss than cows with lower (range 6,857-9,000 kg) milk yield per lactation. Cows with retained placenta were 1.2 times more likely to have fetal loss than cows without this reproductive disorder. Cows suffering premature births had 1.2 greater ($p<0.05$) risk of suffering fetal losses than cows with normal calving and cows carrying twins had more than twice the odds of losing their fetuses than cows carrying single fetuses.

Fetal loss was not associated with the occurrence of a previous abortion and lactation persistency ($p>0.05$). Also, the occurrence of mastitis and uterine diseases did not represent a risk for fetal losses. The interactions between 305-milk yield × peak yield, 305-

Table 1. Risk factors associated (p<0.05) with the occurrence of fetal losses in 14,384 lactating Holstein cows from 2011 to 2015 in a hot environment (25° N).

Variables[a]	n	Fetal losses (%)	OR[c]	95% C.I. OR	*p*
Dry period, days					0.0001
>60	1315/5982[b]	22.0	0.8	0.8–0.9	
<60	2111/8402	25.1	1.0		
BCS at calving					0.0001
>3.0	1184/6567	18.0	0.5	0.5–0.6	
<3.0	2242/7817	28.7	1.0		
BCS 15 d postcalving					0.0001
>2.75	1076/6405	16.8	0.5	0.4–0-5	
<2.75	2350/7979	29.5	1.0		
Peak milk, kg					0.0001
>38	2765/7494	36.9	5.5	5.0–6.1	
<38	661/6892	9.6	1.0		
Retained placenta					0.0001
Yes	613/2325	26.4	1.2	1.1–1.4	
No	2813/12059	23.3	1.0		
305-d milk yield, kg					0.0001
>9,000	2347/7987	29.4	2.1	1.9–2.2	
<9,000	1079/6397	16.9	1.0		
Premature calving					0.0368
Yes	193/713	27.1	1.2	1.0–1.4	
No	3233/13671	23.7	1.0		
Number of offspring					0.0001
2	54/174	31.1	2.4	2.0–3.1	
1	2267/14210	15.9	1.0		

[a]BCS=body condition score (scale 1.0 to 5.0 units). OR: odds ratio. [b]Pregnancy losses/total pregnant cows in each category of animals. [c]OR: odds ratios measure how much more or less likely the outcome is among variables with a given risk factor, compared with those without it, or reference category (odds ratio of 1.0).

milk yield × body condition score at parturition, days dry × peak yield, days dry × body condition score at parturition and BCS at parturition and retained placenta were significant (p<0.05) for the occurrence of fetal losses. The histogram describing the percentage of fetal losses throughout gestation exhibited a significant (two-sided p<|Z| 0.001) bimodal distribution with two well-defined peaks at around 45 and 220 days of gestation (median=131, inferior quartile=73, superior quartile=188; Figure 1).

Discussion

In this study, cows with long dry periods were less prone to fetal loss rate compared with cows with dry period ≤60 days. This response is not clear because dry periods greater than 60 days have led to higher serum non-esterified fatty acids, β-hydroxybutyrate, and lower serum insulin and glucose concentrations postpartum, which indicates a poorer energy balance status compared to cows with shorter dry periods (Weber *et al.*, 2015). Oppositely, cows with short dry periods (35-40 days) have greater dry matter intakes, better reproductive performance (Shoshani *et al.*, 2014) and lost less weight post-partum than cows with >60-day dry periods, suggesting a better metabolic state (Jolicoeur *et al.*, 2014). These results, however, are unsure because the improved reproductive function observed with short dry periods is due to the lower milk yield associated with short dry periods (van Knegsel *et al.*, 2014). In fact, when some reproductive variables are adjusted for milk yield, short dry periods actually results in inferior fertility in the subsequent lactation (Kuhn *et al.*, 2006).

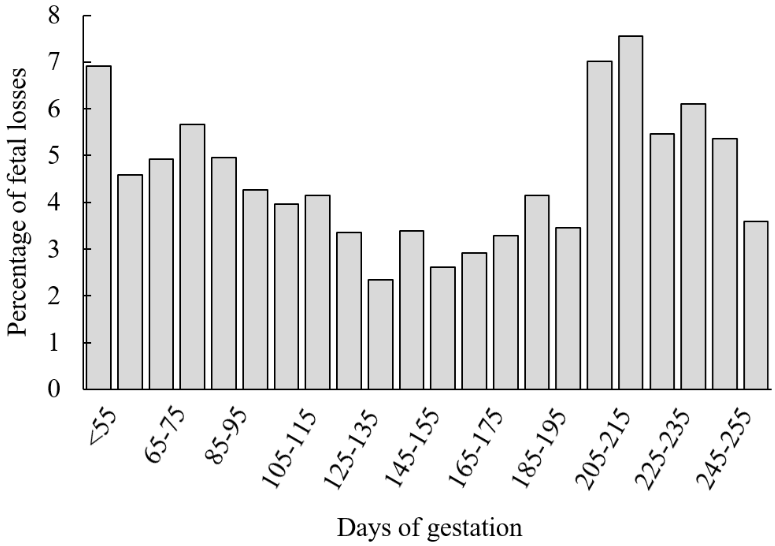

Figure 1. Percentage of fetal losses from 43 to 260 days of pregnancy in 14,384 high-yielding Holstein cows in a hot environment (25° N, 23.5°C mean annual temperature).

Prolonged dry period frequently leads to greater BCS (Weber *et al.*, 2015), but this was not the case in the present study where the difference in BCS of cows with short or long dry period was only 0.04 units. Hence, fetal losses were not associated with body energy reserves in cows with different dry period length.

Low BCS at calving and 15 d postpartum predisposed cows to have higher fetal losses. This is in line with observations of Starbuck *et al.* (2004) who reported that cows in average body condition (2.75–3.25) maintained 92.1% of pregnancies whereas those with lower condition (≤2.50) maintained 84.2% of pregnancies during weeks 5–9 of gestation.

These data demonstrate that energy status is an important factor regulating the survival of fetuses. Fat mobilization to meet energy requirements during early lactation is unavoidable because of insufficient feed intake in high-yielding dairy cows (Wheelock *et al.*, 2010). This loss of weight during the first months of lactation, particularly in cows with low body energy reserves can exacerbate the negative correlation with progesterone secretion, which is harmful to fetal survival (Grimard *et al.*, 2006). Cows with lower BCS would be expected to eat more, which increases the metabolism of progesterone and results in lower plasma concentrations of this hormone (Rabiee *et al.*, 2002). Additionally, low BCS is associated with low-quality embryos (Carvalho *et al.*, 2014) and may be long-term carry-over effects of low body energy reserves on the impaired development of fetuses.

Cows with peak milk yield >38 kg and 305-d milk yield >9,000 kg were more likely to have a fetal loss. It has been shown that very high milk production at the beginning of lactation induce a physiological state of negative energy balance because milk yield, milk proteins, fat and lactose increase rapidly and exceed feed intake (Bertoni *et al.*, 2009). During peak lactation, over 80% of the available glucose in the body is partitioned to the mammary gland for milk synthesis (Hocquette & Bauchart, 1999). Additionally, the majority of fats mobilized from adipose tissue contribute to milk fat synthesis (Grummer, 2008). This situation leads to a decline in cow fertility (Walsh *et al.*, 2011) with fetal losses as one of the major causes of reproductive failure.

The higher fetal losses in cows experiencing retained placenta could be the result of failure of complete uterine recovery and subsequent subclinical endometritis. This condition has been associated with an increase of late embryo/early fetal loss (Lima *et al.*, 2013). Additionally, uterine diseases also modulate the endocrine function of the uterus and ovary, which would hamper fetal development (Dobson *et al.*, 2007).

The first peak of fetal losses observed in the present study (around 45 days) is in line with various previous observations where early fetal losses range between 12 and 20% (Starbuck *et al.*, 2004; Pontes *et al.*, 2015). The second peak of fetal losses occurred in the third trimester of gestation, which is not in line with other reports where it was found that mid-to-late fetal losses were lower than those occurring in early pregnancy in lactating cows (Jousan *et al.*, 2005). Most late-term abortions are caused by infectious diseases, but in the current study, a good vaccination effort directed to abortigenic diseases for dairy cows was implemented, although this does not rule out the possibility of infectious diseases for which cows were not immunized. Therefore, causes of abortions around 220 days of pregnancy remain unclear. This high increment of fetal losses in late-gestation could be due to intense ambient thermal stress (Mellado *et al.*, 2016) via its actions to compromise placental weight and mass (Dunlap *et al.*, 2015), which harm normal placental vascular development and placental inefficiency (Marai *et al.*, 2007), and finally intrauterine growth restriction (Regnault *et al.*, 2002), or to a diverse bacterial species associated with opportunistic infections of the placenta and fetus resulting in abortion (Anderson, 2007). Another possible cause of fetal losses at the end of gestation could be the presence of *Neospora caninum* in the herd (Klauck *et al.*, 2016). This protozoa causes abortion due to tissue destruction in the fetus, the maternal immune response, placental inefficiency due to inflammation, or a combination of these responses (Dubey *et al.*, 2006). Despite a preparturition and then yearly vaccination against *Brucella abortus*, this disease is present in this herd (Mellado *et al.*, 2014), therefore, this disease could be another possible cause of late fetal losses in the present study.

In the present study, the occurrence of premature parturition was associated with greater odds of fetal losses. A plausible explanation for this response is the presence of cows infected with *Neospora caninum*, a widespread disease in northern Mexico (Salinas *et al.*, 2005) that causes calves to be born prematurely (McAllister *et al.*, 2000). In the present study, fetal losses were aggravated with multiple fetuses as compared to a single fetus, despite the fact that bovine females had the uterine capacity to support two fetuses. These findings agree with other studies where the survival of single pregnancies is better than that of twin pregnancies (Silva-Del-Río *et al.*, 2009; Mellado *et al.*, 2016).

As twinning is a consequence of higher potential for milk yield (Macmillan *et al.*, 2018), it seems that the higher fetal losses in cows bearing twin pregnancies are mediated by metabolic stress associated with higher milk yield (Weber *et al.*, 2013). In high-yielding dairy cows, the increased body tissue mobilization and an increased metabolic rate emit metabolic sensory signals that negatively affect reproduction (Chagas *et al.*, 2007).

These findings indicate that higher peak milk yield and 305-d milk production correlates with an increased risk of fetal losses. These results also show that, under the present conditions, it is necessary to maintain BCS at 3.0 units or greater at calving in order to reduce fetal losses and that the occurrence of retained placenta, twin pregnancies and short days dry are important indicators to identify cows at risk for fetal losses. Finally, these observations show that fetal losses under the warm weather of the present study are equally likely at the beginning or late stages of gestation in well-managed high-yielding Holstein cows.

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