Spanish Journal of Agricultural Research
15(2), e0403, 8 pages (2017)
eISSN: 2171-9292
https://doi.org/10.5424/sjar/2017152-10293
Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria, O.A, M.P. (INIA)

RESEARCH ARTICLE

OPEN ACCESS

Prevalence and risk factors for stillbirths in Holstein cows in a hot environment

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Abstract

Risk factors for stillbirth were studied in a dairy operation in northern Mexico (25°N). Data set consisted of 29406 full term calving records. Factors affecting stillbirths were analyzed using a step-wise multivariable logistic regression models. The predictive indicators of stillbirth risk were: temperature-humidity index (THI) during pregnancy and at calving, season of calving, calf birth weight, gestation length, semen characteristics (conventional or sexed), gender of calves, hour of calving and type of parturition (normal or dystocic). Throughout the study period, 7.3 (95%, confidence interval= 7.0–7.6) of every 100 calving events had a stillborn calf. Stillborns were higher with severe dystocia compared with non-assisted births (29.0% *vs*. 6.2%, $p<0.0001$) and calves with birth weights <35 kg compared with heavier calves at calving (19.3% *vs*. 2.3%, $p<0.0001$), and was lower in calves whose gestation length was >278 d compared with calves with shorter gestation periods (2.8% *vs.* 30.0%, $p<0.0001$). Cows in a severe state of heat stress prenatally and at birth (THI >83 units) had 1.3 higher risk of stillbirths than cows suffering reduced heat stress ($p<0.0001$). Evidence for a greater ($p<0.001$) stillbirth rates in cows with parturitions between 18:00 and 19:00 h compared with cows calving during other hours of the day was found (9.1% *vs.* 7.1%). Together, these results demonstrate that ameliorating heat stress during the peripartum period is an important management practice to reduce stillbirths in Holstein cows in this warm climate. Additionally, a greater attention of parturition around sunset can lower the current stillbirth rates.

Additional keywords: heat stress; sexed semen; birth weight; dystocia; gestation length

Abbreviations used: AI (artificial insemination); GnRH (gonadotrophin releasing hormone); RH (relative humidity); THI (temperature–humidity index)

Authors' contributions: Conceived and designed the experiments, and analyzed the data: MM and JEG. Performed the experiments: MIC, UMC, EC and LAR. Wrote the paper: MM.

Citation: Mellado, M.; Chávez, M. I.; Macías-Cruz, U.; Avendaño-Reyes, L.; Carrillo, E.; García, J. E. (2017). Prevalence and risk factors for stillbirths in Holstein cows in a hot environment. Spanish Journal of Agricultural Research, Volume 15, Issue 2, e0403 https://doi.org/10.5424/sjar/2017152-10293

Received:04 Aug 2016. **Accepted:** 25 May 2017

Funding: The authors received no specific funding for this work.

Competing interests: None of the authors has any financial or personal relationships that could inappropriately influence the content of this paper.

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Introduction

Considering the production-reproduction antagonism and the increased culling rates of cows in intensive dairy operations (Chiumia *et al.*, 2013; Berry *et al.*, 2016), newborn calf survival is critical for maintaining the profitability of dairy herds. Loss of calves at parturition also represent significant costs because this periparturient disorder often results in compromised reproductive performance, reduced milk yield and longevity of cows (Berry *et al.*, 2007; Bicalho *et al.*, 2008).

Recent studies show that the prevalence of perinatal mortality in dairy calves is increasing, particularly in primiparous Holstein cows (Mee *et al.*, 2014). Difficult calving is often the primary cause, but only accounts for approximately 50% of stillbirths causes (Eriksson *et al.*, 2004; Barrier *et al.*, 2013). Thus, a substantial part of the stillbirths does not coincide with calving difficulties (Mee *et al.*, 2008).

Stillbirth is usually multi-factorial in nature. Some risk factors that have been linked with this condition is twinning (Silva del Rio *et al.*, 2007; Waldner, 2014), parity and dystocia (Meyer *et al*., 2000), calf gender (Johanson & Berger, 2003), calf birth weight (Johanson & Berger, 2003), serum hormones alteration (Kindahl *et al*., 2002) and calves management (Palombi *et al*., 2013), among others. Other congenital (Berglund *et al*., 2003), infectious (Grooms, 2006), nutritional, body energy reserves (Chassagne *et al*., 1999) factors can contribute to the occurrence of stillborn calves. Additionally, abortive microorganisms such as *Leptospira* spp (Parvez *et al*., 2015), *Brucella* spp, *Neospora caninum* (Brickell *et al*., 2010), bovine viral diarrhea and infectious bovine rhinotracheitis (Berglund *et al*., 2003), could cause weak calves at calving compromising calves' survival within the 24 h of life. However, around 35% of the time the cause of death of a newborn, during or within the first 24 h after birth, cannot be determined (Berglund *et al*., 2003).

Heat stress disrupts both physiological processes and reproductive performance of high-yielding dairy cows (De Rensis *et al*., 2015). The consequences of this thermal stress are not only manifested during periods of high ambient temperature, but present long-lasting effects on the fertility of the dairy cow (García-Isperto et al., 2006, 2007). Recent evidence shows that offspring from pre-partum heat-stressed cows have impaired cell-mediated immune function and compromised passive immunity (Tao & Dahl, 2013), as well as a reduced secretion of prolactin, insulin and insulin-like growth factor (Guo et al., 2016), which could be linked to the occurrence of stillbirths. A missing piece of the stillbirth puzzle, thermal stress during the peripartum period, has not been adequately investigated relative to stillbirth incidence. To address this gap in our understanding of stillbirth problems, the objective of this study was to test the hypothesis that high ambient temperature during the peripartum period would increase the rate of stillborn calves. An additional objective was to investigate birth weight, gestation length, semen characteristics (conventional or sexed), gender of calves, parity and type of parturition (normal or dystocic) as predictive indicators of stillbirth risk under heat stress for the most part of the year.

Material and methods

Herd management

Data for this retrospective field study were obtained from a commercial dairy herd (5,500 Holstein cows) located in northeastern Mexico (25°N, elevation 1140 m, mean annual temperature 23.4ºC, mean annual rainfall 230 mm). Cows were housed outdoors all year in open-lot, dirt floor pens with sufficient shade structures in each pen and with a feed alley. Cows were fed a total mixed ration (51% forage, 49% concentrate) formulated to meet or exceed the nutrient requirements for a lactating Holstein cow weighing 650 kg and producing 40 kg of 3.5% fat-corrected milk (NRC, 2001). Cows were fed *ad libitum* for a daily feed refusal of about 10% of that offered. Cows were milked three times per day and were fed following each milking. Lactation number of cows included in the study varied from one to eight; with body condition score of cows at calving ranging from 3.0 to 3.75 (scale 1 to 5; Edmondson *et al*., 1989). The 305-day rolling herd average for this dairy operation was about 9,850 kg. Heifers must have reached 14 mo of age and must have weighed 345 kg before they were inseminated.

Heifers and cows were routinely vaccinated against diseases that hamper reproductive functions, such as infectious bovine rhinotracheitis, bovine viral diarrhea, para-influenza, bovine respiratory syncytial virus, leptospirosis and brucellosis. The herd's veterinary examined fresh cows to detect and treat cows with postpartum reproductive disorders, such as retained placenta and clinical metritis. The voluntary waiting period was 50 d post-calving, after which cows were submitted for artificial insemination (AI) when spotted in estrus. Cows not pregnant around 160 days in milk or with more than three services without subsequent calving and no clinically detectable reproductive disorders, were submitted to the Ovsynch protocol (gonadotrophin releasing hormone [GnRH] injection seven days before prostaglandin $F_{2\alpha}$; a second GnRH injection 48 to 56 h after prostaglandin; and then timed AI 18 h later).

Commercial frozen-thawed semen from multiple sires from the USA was used across all months of the year. Virgin heifers were artificial inseminated with sexed semen at first estrus, and if not pregnant, conventional semen was used in subsequent inseminations. Pregnancy was detected by rectal palpation of the uterus and its contents about 45 days post-AI. Farm personnel recorded each calving event including date of calving, hour of calving, birth weight (up to 12 h after calving), gestation length (number of days from last AI to calving) dystocia (considerable force used to deliver the calf), calf gender, and occurrence of stillbirths (defined as a calf dead at birth, or that died within 24 h of calving).

Data recording and structure

This study followed a retrospective observational study design. A total of 29,406 full term calving records between February 1, 2009, and November 25, 2014, were used. Data from primiparous and multiparous cows were used and data were restricted to single calvings (597 twin births were excluded). Farm personnel recorded each calving event on a form used in this dairy operation. Data were recorded manually and then transferred to the AfiFarm integrated herd management software (SAE, Hazafom, Afikim, Israel). Information recorded included dam parity, date of calving, occurrence of dystocia (manual pull, chain pull, or use of a calf-jack about 2 h after the appearance of the calf's feet), calf gender, calve morality at 24 h post-calving, and calf identification. Date of calving was used to allocate a season of calving. Seasons were categorized as winter (December through February), spring (March through May), summer (June through August), and autumn (September through November). For the analysis, parity was categorized as primiparous and multiparous.

Climatic data

Climatic data were obtained from a meteorological station located 2.5 km north from the dairy operations for the duration of the study; thus, these data accurately reflect weather conditions on the farm. Information consisted of daily maximum temperatures in °C and relative maximum humidity. Air temperature was recorded continuously and compiled hourly with a mercury thermometer freely exposed to the air but shielded from radiation and moisture. This information was used to calculate the daily temperature–humidity index (THI) using the following equation (Mader *et al.,* 2006):

$$THI = (0.8 \times T) + [(\%RH / 100) \times (T - 14.4)] + 46.4$$

where T= temperature. This formula uses maximum air temperature (ºC) and the relative humidity (RH). The RH is divided by 100 to express the percentage in decimals.

Statistical analyses

The UNIVARIATE statement of SAS (SAS Inst. Inc., Cary, NC, USA) was used to obtain the main stillbirth rate and 95% confidence interval. Stillbirth rates for all statistically significant variables were calculated with the FREQ procedure of SAS. Logistic regression models were developed to estimate odds ratios and 95% confidence intervals.

To analyze risk factors contributing to the occurrence of stillbirths (binary trait), a multivariate logistic regression model of SAS was used, applying a backward stepwise logistic procedure to eliminate all non-significant variables. These were continuously removed from the model by the Wald statistic criterion if the significance was greater than 0.20. The preliminary full model included the following potentially explanatory variables of interest: parity, THI at calving and at 7th and 8th months of gestation (greater than 83, between 73 and 83 and lower than 73 units), dystocia (dichotomized variable), season of calving, gender of calves, birth weight of calves (greater or less than 35 kg), gestation length (greater or less than 278 days) and type of semen (sexed or conventional; only for primiparous cows; n= 1184 AI with sexed semen). The upper cut-off point of 83 units for THI was selected because at this value Holstein cows experience severe heat stress. This THI index corresponds to 40°C at 20% humidity, 36°C at 38% humidity, or 32°C at 65% humidity.

No significant interactions were found between sources of variation, therefore, the final model included only main effects and year of calving as covariate. Linear regression models (proc REG and proc CORR of SAS) were used to assess the association between gestation length and THI at the final stages of gestation and gestation length and calf birth weight. Trends in the rates of stillbirths as a function of hour of calving were tested with the asymptotic Cochran-Armitage trend test with PROC LOGISTIC of SAS.

Results and discussion

Throughout the study period, 7.3 (2138/29405; 95% CI 7.0–7.6) of every 100 calving events had a stillborn calf. This value falls within the expected incidence rate of 7% observed in other intensive dairy operations in temperate zones (Chassagne *et al*., 1999; Johanson & Berger, 2003; Kayano *et al.,* 2016). In hot environments, the prevalence rates for stillbirths in Holstein cows range from 3 to 15 (Hossein-Zadeh *et al*., 2008; El-Tarabany, 2015). Significantly more cows suffering moderate heat stress (THI 73 to 83 units) during the eighth month of gestation presented stillbirths (Table 1, $p<0.01$) compared to cows not experiencing heat stress in the final stages of gestation. Additionally, stillbirths were more common if cows were exposed to moderate hyperthermia at calving than cows not experiencing heat stress at delivery. The percentage of pregnancies ending in stillbirths did not differ significantly between cows with moderate heat stress (THI 73 to 83 units) during the seventh month of gestation that in the group of cows not suffering heat stress at this stage of pregnancy (Table 1). These data showed that even moderate heat stress did not allow cows to restore their thermal balance, presumably causing physiological changes that had an impact on the survival of calves at parturition or shortly after birth.

Table 1. Risk factors related to climatic conditions during late pregnancy and parturition for the occurrence of stillbiths in 29,406 lactating Holstein cows from 2010 to 2014 in a hot environment (25°N; 23.3°C mean annual temperature).

Variables	n	Stillbirths (%)	OR	95% CI OR	*p*
THI 7 months gestation					
>83	11901	8.1	1.2	1.1–1.4	0.0001
73-83	13199	6.7	0.9	0.8–0.9	0.79
<73	4306	6.8	Referent		
THI 8 months gestation					
>83	10547	8.3	1.3	1.2–1.4	0.0001
73-83	13986	7.0	1.2	1.1–1.4	0.002
<73	4872	5.9	Referent		
THI at parturition					
>83	8882	8.6	1.3	1.2–1.4	0.0001
73-83	14691	6.9	1.1	1.0–1.2	0.01
<73	5832	6.3	Referent		
Gestation length					
<278 days	4801	30.0	9.0	7.9–10.2	0.0001
>278 days	24605	2.8	Referent		
Birth weight, kg					
<35	8589	19.3	6.4	5.5–7.4	0.0001
>35	20817	2.3	Referent		
Type of parturition					
Dystocic	1365	29.0	24.5	20.6–29.1	0.0001
Normal	28041	6.2	Referent		
Gender					
Females	15259	7.0	0.6	0.5–0.7	0.0001
Males	14147	7.6	Referent		

THI: temperature-humidity index; .OR: odds ratio; CI: confidence interval

Cows experiencing severe heat stress at calving (THI > 83) were 1.3 times more likely to have stillborn calves than cows with less severe climate conditions at parturition (Table 1). Likewise, cows undergoing extreme heat stress at the 7th and 8th month of pregnancy were more likely to deliver stillborn calves than cows without heat stress during the final months of pregnancy. These results suggest that under the climatic conditions of the present study, in utero heat stress in late gestation resulted in a greater incidence of stillbirths in Holstein cows, relative to cows that did not experience hyperthermia at the end of pregnancy. The way hot weather increases the risk of stillbirths is not quite clear, as no controlled experiments to find out this association have been carried out. Given that calves developing in the uterus of heat-stressed dams are exposed to increased maternal respiration rate and core temperature during the final weeks of pregnancy, their structural and physiological integrity may be compromised. The homeokinetic changes to regulate body temperature of cows suffering heat stress provoke a redistribution of blood flow from the body core to the periphery, which reduces perfusion of the placental blood vessels (Hansen, 2009). Additionally, heat stress during gestation can compromise placental development, which results in fetal hypoxia, malnutrition, and eventually fetal growth impedance (Tao *et al*., 2012). Maternal hyperthermia also desensitizes a calf's stress response and alters the fetal development by reducing the secretion of insulin-like growth factor-I, prolactin, and insulin (Guo *et al*., 2016). Additionally, maternal heat stress during late gestation alters blood metabolite profile and increases non-insulin dependent glucose uptake (Monteiro *et al*., 2016a) which eventually negatively affects the survival of calves (Monteiro *et al*., 2016b).

Thus, extreme thermal stress in uterus seems to alter the feto-maternal interaction compromising the fetus development and even can cause the demise of the fetus between 43 and 260 days of pregnancy as it has been observed by Mellado *et al.* (2016).

Gender of the calf was associated with the occurrence of stillbirths, as bull calves were more (p<0.001) likely to be stillborn than heifer calves (Table 1). These results are consistent with several studies where it has been reported that male calves have higher odds of stillbirths than female calves (Maltecca *et al*., 2006; Dhakal *et al.*, 2013). In contrast to these results, Meyer *et al.* (2001) observed that female calves had 12% higher odds for stillbirth than male calves if they were from multiparous cows, but 7% lower odds if they were born from primiparous cows. Olson *et al.* (2009) found that Heifer calves were as likely as bull calves to be stillborn. Causes for these apparent contradictions are not clear, although these differences could be explained by the inconsistent definition of stillbirths among studies and the difference number of observations used in different studies.

Cows with gestations >278 were at decreased risk of stillborn calves than cows with pregnancies shorter than 278 d (Table 1). These results closely coincide with results of Meyer *et al.* (2000) who observed that stillbirth rate increased from 23.8% among calves born at or above the mean gestation length to 55.3% for those calves born −15 to −12 d below the mean gestation length. However, gestation lengths above the average gestation period for Holstein cows also results in increased stillbirths which gave a curvilinear relationship between gestation length and incidence of stillbirths (Fig. 1a).

This tendency closely coincides with other studies with dairy calves (Johanson & Berger, 2003). THI at

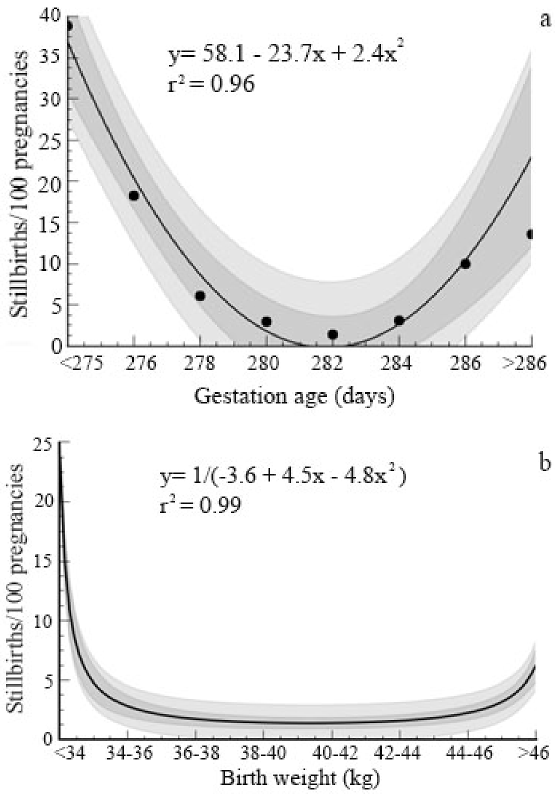

Figure 1. Effect of gestation length (a) and birth weight (b) of Holstein calves on the occurrence of stillbirths in a hot environment (25°N, mean annual temperature 23.4ºC). Darker bands are 95% confidence intervals for predicted values. Lighter bands are 95% confidence intervals for real values.

seven and eight months of pregnancy and at parturition was not associated with gestation length (r= -0.02 to -0.04), therefore, clearly climatic conditions have no influence on the duration of pregnancy. The risk was much higher for calves born after a short gestation than a prolonged gestation, apparently due to organ immaturity (Briana & Malamitsi-Puchner, 2013; Sangild *et al*., 2013; Caminita *et al*., 2015), apparently due to reduced exposure to cortisol. This hormone promotes maturation of fetal organ systems while diminishing the rate of proliferation (Murphy *et al*., 2006). This variable has been considered the next most important predictor of stillbirth after dystocia (Meyer *et al.*, 2000).

Lighter calves had six times the odds of being stillborn than heavier calves at birth (Table 1). Other studies have reported a trend for higher mortality risk when calf birth weight was small (Tarrés *et al*., 2005). Conversely, Linden *et al*. (2009) did not find an association of calf birth weight with stillbirth incidence in Holstein cows. Calves developing in the uterus of heat-stressed dams, as was the case in the present study, are unprotected from the increased core temperature during the end of gestation. This results in a negative consequence in the calf, such as lower birth weight (Dahl *et al*., 2016), and there is a consensus regarding the negative impact of low birth weights on calf survival (Bleul, 2011). Also, gestation length is typically reduced by 4 to 5 d with hyperthermia during the dry period, which may account for smaller calf size with lower vitality (Tao & Dahl, 2013). Gestation length significantly explained variation (p<0.01) for birth weight, with an increase of 0.37 ± 0.004 kg of birth weight per day of gestation, which closely agrees with observations of Dhakal *et al*. (2013). As birth body weight increased or decreased, the risk of stillbirths increased in a curvilinear manner (Fig. 1b). From <34 kg of birth weight, there was a strong change in the increased risk of stillbirths. Then, from >46 kg, each kg increase leads to increasing risk of stillbirths.

Odds of occurrence of stillborn calves were 25 times greater for cows with dystocic parturition than cows calving unaided. This value is close to that reported by Lombard *et al*. (2007) with mostly Holstein cows in intensive dairy operations. In cattle, dystocia has been found to be related to several negative outcomes, such as survival of newborn calves (Eriksson *et al.*, 2004; Bicalho *et al*., 2008; Barrier *et al*., 2013). This is so because dystocial calves normally experience higher physiological stress, acidosis and hypoxic state which result in lower vigor (Barrier *et al*., 2012; Kovács *et al*., 2016) and consequently in reduction in the transfer of passive immunity, as well as important metabolic changes (Barrier *et al*., 2013; Vannucchi *et al*., 2015). Stillborn calves from dystocic parturition not necessarily exhibit specific types of trauma, but do exhibit larger lesions than their eutocic counterparts, indicating that they experienced greater trauma during delivery (Barrier *et al.*, 2013). Nonetheless, it should be stressed that a major proportion of stillborn calves results from normal calvings (Berglund *et al*., 2003; Benjaminsson, 2007).

The use of sexed semen, season and parity of dam were not significant sources of variation for stillbirths. Of note, parity of dam has been consistently found an important risk factor for bovine stillbirths, with primiparous being at a higher risk of stillbirths than pluriparous (Meyer *et al*., 2001; Berry *et al*., 2007; Bicalho *et al*., 2008; Uematsu *et al*., 2013). The lack of effect of this variable on stillbirths in the present study in unknown, although the causes of stillbirths vary markedly from farm to farm.

There was a distinctive increase in stillbirth rates when parturitions occurred between 18:00 and 19:00 h, compared with all other hours of the day (Fig. 2). The factors responsible for this trend are unclear. One possible explanation could be just a lower attention of cows calving at this time of the day. Insufficient monitoring around parturition has a negative effect on perinatal mortality (Gundelach *et al.*, 2009). Given that the results of the present study point toward a connection between high ambient temperature and a higher occurrence of stillbirths, it could be that the accumulated heat load throughout the day by cows about to give birth, predisposes these animals to give birth to stillborn calves with parturitions at sunset.

As conclusions, the occurrence of stillbirths on this dairy farm was associated with either moderate or extreme heat stress during the peripartum period, with negative impacts from the seventh month of pregnancy until calving. Thus, ameliorating heat stress for heifers and cows before parturition could reduce stillbirth incidence. Dystocia was another important variable affecting of whether a calf would be alive or stillborn,

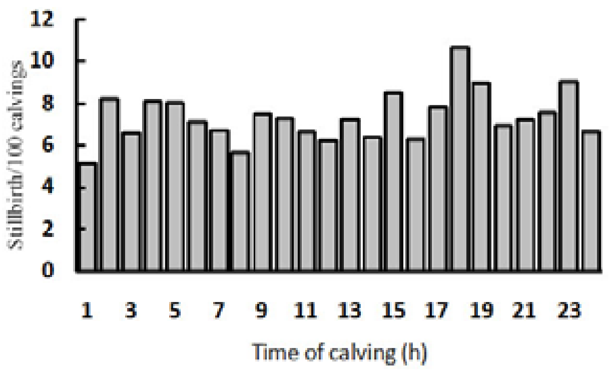

Figure 2. Percentage distribution of stillbirths in Holstein cows in a hot environment by hour of the day of delivery (n= 29,406 full term calving records, excluding twins).

therefore, intervention to reduce difficult births should reduce the incidence of this problem. Both extreme birth body weight and gestation length increased the rates of stillbirths, which suggests that pre-term calves should get a special look at birth. The herd manager of this dairy operation should pay greater attention to cows giving birth at sunset because at this time of the day stillborn calves are more common.

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