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Gestation Length is Associated With Early-Life Limb Deformities in Thoroughbred Foals

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ABSTRACT

Flexural and angular limb deformities (LD) are an important cause of early-life morbidity and mortality/euthanasia in Thoroughbred foals. The majority are congenital in origin but, to date, their precise aetiology is poorly understood. We hypothesized that maternal- and pregnancy-level factors, particularly those with potential to influence in-utero growth and development, could play an important role. The aim of this study was therefore to investigate associations between such factors and early-life LD in Thoroughbred foals. A birth cohort was established on seven farms across the United Kingdom and Ireland and details of veterinary interventions for LD in foals in the first six months of life prospectively recorded. Details of dams' signalment, breeding history and reproductive and veterinary history in the breeding season(s) of interest were retrieved retrospectively from stud farm and veterinary records. Associations between mare- and pregnancy-level factors and LD in offspring were assessed using multivariable logistic regression. Records were available for 275 pregnancies in 235 mares, over two breeding seasons. Pregnancies resulted in the birth of 272 live foals, 21% of which (n = 57/272, 95% CI, 16–26) required veterinary intervention for LD in the first six months of life. Odds of LD decreased by 4% per day increase in gestation length between 314 and 381 days (OR 0.96, 95% CI, 0.93–0.99, P = .01). Longer gestation length appears to reduce the odds of early-life LD, including within the normal range of gestation length for Thoroughbred foals. Further work is required to elucidate biological mechanisms behind this association.

1. Introduction

Recently published studies have highlighted congenital angular and flexural (contracture and laxity) limb deformities (LD) as an important cause of early-life morbidity [1,2] and mortality/euthanasia [3,4] in Thoroughbred foals. It has been estimated that up to 20% of foals are affected to the extent that some form of intervention (exercise restriction, farriery and/or veterinary) is required during the first months of life [1,2] Treatment and management of such cases is both costly and time consuming. Affected foals require additional farm resources in terms of stabling and exercise restriction, and frequently incur costs of remedial farriery and veterinary interventions such as medical therapies and bandaging/splinting, alongside surgical correction in the most severe cases [4–7]. In a survey to UK Thoroughbred breeders, a loss of yearling sales value was reported in just under half of all individuals treated for these conditions [8]. This raises additional economic concerns, particularly in the current financial climate where latest industry figures estimate the median yearling sale to make a loss of £33,000 [9].

Factors such as uterine positioning, abnormal fetal development and disease or malnutrition of the mare have been postulated as possible causes of congenital LD [5,6] but, to date, the exact aetiology remains poorly understood. A higher prevalence of conformational defects and nonseptic orthopedic disease have been described in heavy Thoroughbred foals [10]. Mare-level factors such as age and parity, and pregnancy-level factors such as

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gestation length have previously been shown to influence both in-utero growth and foal birthweight [11–16], and could therefore also affect offspring LD status.

Epidemiological studies, such as the present work, provide an opportunity to evaluate associations between maternal- and pregnancy-level factors and early-life LD in foals under field conditions. Findings could help inform future research, further understanding of the aetiology of LD, and inform management strategies aimed at reducing their occurrence. The main objective of this study was therefore to utilize available data from a birth cohort study to investigate associations between mare- and pregnancy-related factors and LD requiring veterinary intervention in foals between birth and 6 months (180 days) of age.

2. Materials and methods

Ethical approval was granted by the Royal Veterinary College's Clinical Research Ethical
Review Board (URN: 2018 1843).

2.1. Study design

A Thoroughbred birth cohort was established on seven farms across the United Kingdom (UK) and Ireland. All foals born over a two-year study period from the January 1, 2019 to the December 31, 2020 were recruited to the study and under observation from birth until leaving the farm to enter training or study exit. Farms recorded daily information on foals/yearling management practices alongside any episodes where foals/yearlings were examined by a veterinary surgeon or farrier, or received any medication for any reason. Farms also provided access to stud and veterinary records to allow for the collection of retrospective data on mare reproductive management and gestational exposures, and further details of veterinary interventions and medication. For the purposes of this study, the unit of interest was the pregnancy resulting in the birth of a live foal in each season. Mare- and pregnancy-level exposures were defined as variables related to the mare or the pregnancy that were recorded between the date of last service and the date of foaling (gestation). The follow-up period for foal outcomes was from birth to 180 days of age or study exit.

Detailed methods of the overarching Thoroughbred birth cohort project, of which this work forms one part, are described elsewhere [2].

2.2. Sample size calculation

Sample size calculations were carried out in Stata (Release 16, StataCorp LP, College Station, TX). For the purposes of the overarching research project, using a survival analysis approach to investigate risk factors for early-life disease or injury a total sample size of 220 foals to be monitored up to entering race training was required. This assumed a 25% outcome prevalence, study entry over a 6-month period, an average follow-up time of 20 months, median survival in the "unexposed" of 20 months and a hazard ratio of 2. For the present study using a "case-control" approach to identify risk factors for LD, it was estimated that an odds ratio of at least 2 could be detected with 80% power in 270 pregnancies, assuming an exposure frequency in "healthy" foals of 35% and an alpha error of 5%.

2.3. Data collection and processing

Foals' dams were identified, and their stud and veterinary records retrieved. Where available, data were collected on mares' signalment, previous breeding history, reproductive management during the breeding season(s) of interest, along with pregnancy-level factors such as service and foaling date(s), covering stallion, dystocia and details of any episodes of illness or injury that required veterinary intervention during gestation and any medications administered. All data were entered into a purpose-designed form within a custom Access database (Microsoft Access 2016, Microsoft Corporation). Data on mare age, number of previous live foals, status at the start of the breeding season and covering stallion were verified with Weatherbys' "return of mares" publications [17] and the Racing Post website [18]. Status at the start of the breeding season was categorized as foaling (mare produced a live foal from the previous breeding season), maiden (mare had never produced a live foal) and no live foal (mare had failed to produce a live foal in the previous season but had previously produced one or more live foals). Number of cycles covered to conception was calculated as the number of oestrus cycles in the breeding season of interest during which the mare was covered prior to a positive pregnancy diagnosis. Gestation length was calculated as foaling date minus last service date. Episodes of mare illness and injury during gestation were categorized, using diagnoses and clinical descriptions recorded in veterinary records. To aid this process, case definitions were created based on existing literature [19–22] (Supplementary Table 1). Medications prescribed to pregnant mares were initially described by active ingredient, then active ingredients were grouped by category, for example antibiotic or non-steroidal anti-inflammatory drug (NSAID). The Veterinary Formulary [23] was used to verify information.

A coded entry was made, by farm personnel in a data collection booklet provided for the purpose of the study, on any date a foal was examined by a veterinary surgeon for any reason. Further details of these events, including all clinical information provided by the attending veterinary surgeon, were collected retrospectively from stud and veterinary records. Foal outcome events were identified from all available records within the follow-up period (birth to 180 days of age). A case of LD was defined as a foal in which a veterinary surgeon (i) made diagnosis of a flexural (contracture or laxity) and/or angular deformity of any limb(s) and (ii) recommended/prescribed at least one of the following interventions: exercise restriction, medication, remedial farriery, splinting/bandaging and/or surgical correction. To aid identification of cases, key descriptive terms for LD were created using existing literature [5–7] (Supplementary Table 2). Foal age at the time of the event was calculated as the date of the event minus date of birth.

All veterinary and medication data were categorized independently by two veterinary-qualified reviewers (R.M., J.C.A.); in case of disagreement a third reviewer (K.V.) was available so a final consensus decision could be made.

2.4. Statistical analyses

Analyses were carried out using Stata (Release 16, StataCorp LP, College Station, TX). For the purpose of analyses in this study, only the first veterinary-attended episode of LD in a foal was included. Repeated episodes of the same condition requiring veterinary intervention in mares as well as repeat prescriptions of the same medication during gestation were not considered. To describe mare- and pregnancy-level factors, histograms were plotted of continuous data and visually inspected for normality. Mean and standard deviation (SD) were reported for normally distributed data and median and interquartile range (IQR) were reported for non-normally distributed data, as well as the range. Frequencies, proportions and 95% confidence intervals (CI) were calculated for all categorical variables. The frequencies and incidence of LD (number of new cases of LD/number of pregnancies), with 95% CIs, were calculated at various levels of all exposure variables.

Logistic regression was used to investigate associations between mare- and pregnancy-level factors and having at least one episode of LD requiring veterinary intervention in foals. Due to potential data clustering [24] farm, mare and stallion were evaluated by fitting them as random effects into an empty (null) model with the outcome of interest. There was deemed to be evidence of clustering where the likelihood ratio test (LRT) comparing the random effect model to a null model resulted in $P < .05$. In such a case, the variable would be fitted as a random effect in all univariable and multivariable models. Farm was also evaluated as a fixed effect.

From available data collected from dams that produced a live-born foal, a total of 16 exposure variables were evaluated as fixed effects in logistic regression models alongside farm. These included five mare factors (age, number of previous live foals, number of cycles covered before conception, status at the start of the season and month of cover), four pregnancy-related factors (gestation length, dystocia, sex, and breeding season) and seven binary (yes/no) gestational disease/injury and medication factors (mare required veterinary intervention for musculoskeletal disease/injury, for placentitis, for mastitis, mare received antibiotics, NSAIDs, altrenogest or sedative during gestation). The assumption of linearity of association between continuous exposure variables and the log odds of the outcome was assessed; where significant departure from linear trend was identified (LRT $P < .05$) variables were modelled as categorical predictors.

Exposure variables were taken forward to be considered for inclusion in a multivariable model if the univariable LRT $P < .20$. The multivariable model was built using a forward stepwise approach with inclusion based on a LRT $P < .05$. All exposure variables taken forward for multivariable modelling were evaluated for evidence of confounding (estimates changed >20%) and interaction (LRT comparing models with and without the interaction term $P < .05$). If detected, confounders and interaction terms would be reported and retained in the final model.

The predicted mean probability of LD was estimated from the final model using the *margins* command in Stata [25]. Fit of the final model was evaluated using a Pearson's goodness-of-fit test. Statistical significance was set at $P < .05$. Residuals were plotted against predicted values and any influential or outlying points were identified and data manually verified for potential errors.

3. Results

3.1. Description of data

Data were available for 275 pregnancies, carried by 235 mares on seven stud farms over two breeding seasons (three of the seven farms contributed data in the second season, with n = 40 mares conceiving in both seasons). Six farms were based in the UK and one in Ireland. The average number of mares per farm over the two breeding seasons was 34 (SD 22, range 10–104). Median mare age at covering for the 275 pregnancies was 7 years (IQR 5–10, range 3–22). At covering, 18% of mares (n = 48/272, 95% CI, 14–23) were reported to be maidens (never previously bred), 18% (n = 49/272, 95% CI, 14–23) were reported to have failed to produce a live foal from covering in the previous breeding season and 64% (n = 175/272, 95% CI, 58–70) were reported to have produced a live foal as a result of a covering in the previous breeding season.

Seventy-two percent of pregnancies (n = 197/275, 95% CI, 66–77) were conceived in 2018 and 28% (n = 78/275, 95% CI, 23–34) in 2019. Thirteen percent of pregnancies were the result of coverings in February (n = 35/273, 95% CI, 9–17), 29% in March (n = 79/273, 95% CI, 24–35), 38% in April (n = 105/273, 95% CI, 33–44), 18% in May (n = 49/273, 95% CI, 14–23) and 2% in June (n = 5/273, 95% CI, 1–4). Coverings were performed by 89 different stallions; the maximum number of coverings per stallion was 33, the minimum 1 and median 2 (IQR 1–4).

Detailed description of conditions requiring veterinary intervention in the mares and medications prescribed during gestation are reported elsewhere [26]. Dystocia where the mare required significant manual intervention, such that the second stage of labor was prolonged, was reported in 6% (n = 17/275, 95% CI, 4–10) of pregnancies. Mean gestation length was 344 days (SD 11, range 314–381, n = 273). Pregnancies resulted in 138 colts and 137 fillies (n = 197 born in 2019 and n = 78 born in 2020). Three of the 275 foals (1%, 95% CI, 0–3) were reported as having died during or shortly after the process of parturition following premature placental separation and/or dystocia, none of which were reported to have been affected by LD. Of the 272 live foals, 21% (n = 57/272, 95% CI, 16–26) were reported to have been diagnosed with LD that required veterinary intervention at least once between birth and 180 days of age. Seventy-five percent (n = 43/57, 95% CI, 63–87) were described as flexural and 25% (n = 14/57, 95% CI, 15–37) as angular deformities; median age at veterinary intervention was 9 days (IQR 1–19, range 0–132). Table 1 gives a summary of reported presentations of LD. Incidences of LD at the various levels of the predictor variables are reported in Table 2. Further description of LD cases and disease incidence in this cohort are reported elsewhere [2].

3.2. Univariable analysis

Model fit was not improved by inclusion of farm, mare or stallion as a random effect (LRT $P = .10$, $P = .36$ and $P = .92$ respectively) when compared to a null model, therefore simple logistic models were used.

Results of univariable analysis are given in Table 2. Gestation length, farm, mares' previous number of live foals, number of cycles covered prior to conception and dystocia were found to have a univariable $P < .20$ and were therefore taken forward for consideration for inclusion in the multivariable model.

3.3. Multivariable analysis

Following multivariable analysis, only gestation length was found to be associated with the odds of a foal being diagnosed with at least one episode of LD requiring veterinary intervention between birth and six months of age. No confounders or effect modifiers were identified. The odds of LD decreased by 4% per day increase in gestation length between 314 and 381 days, the range observed in this study (OR 0.96, 95% CI, 0.93–0.99, $P = .01$). A plot of the predicted mean probability of LD (predicted prevalence) with 95% CIs, by gestation length, is given in Fig. 1.

Predicted prevalence (mean probability) of LD ranged from around 45% at gestation length of 314 days to around 5% at a gestation length of 381 days. The Pearson's goodness-of-fit test found no evidence ($P = .57$) to reject the null hypothesis that the final model provided an adequate fit to the data.

4. Discussion

Findings from this study have updated current knowledge of the incidence of LD during early-life in Thoroughbreds and reported, for the first time, a continual and decreasing risk of LD with increasing gestation lengths between 314 and 381 days, highlighting potentially important areas for further research into the aetiology of this condition. In the study population, no foals with gestation lengths >360 days required veterinary intervention for LD in the first six months of life. Within the "normal" range of gestation length for Thoroughbreds (320–380 days [27,28]) the fi-

Table 1
Summary of presentations of limb deformities (LD) requiring veterinary intervention between birth and 180 days of age in a cohort of 272 live foals, from 233 mares on seven stud farms in the UK and Ireland over two breeding seasons (n = 194 conceived in 2018 and n = 78 in 2019).

LD presentation	Cases (n = 57)			Live foals (n = 272)			Age (days)	
	n	%	95% CI	n	%	95% CI	Median	IQR
Flexural deformity	43	75.4	62.9–84.8	43	15.7	11.9–20.5	4	1–16
Contracture	*36*	*63.1*	*50.1–74.5*	*36*	*13.2*	*9.7–17.8*	*6*	*1–30*
Laxity	*7*	*12.3*	*6.1–23.2*	*7*	*2.6*	*1.2–5.2*	*4*	*0–16*
Angular deformity	14	24.6	15.2–37.1	14	5.1	3.1–8.4	18	10–30

Abbreviations: CI = confidence interval, IQR = interquartile range.

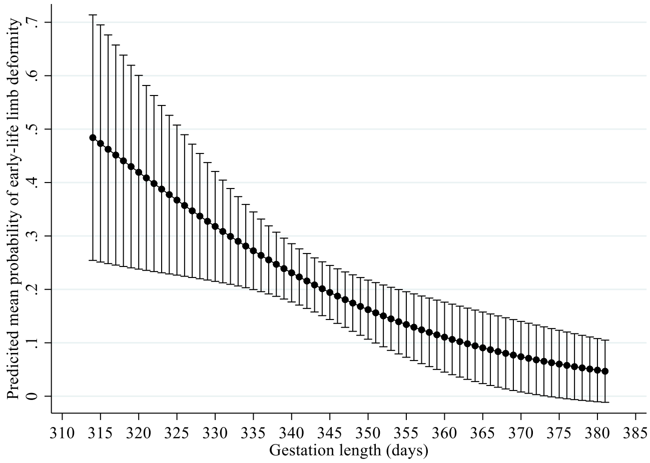

Fig. 1. Marginal predicted mean probability and 95% confidence interval of a foal being diagnosed with a limb deformity requiring veterinary intervention at least once between birth and six months of age by gestation length, for gestation lengths between 314 and 381 days. Calculated using data from 272 live-born Thoroughbred foals from 233 mares on seven farms in the UK and Ireland over two breeding seasons (n = 194 conceived in 2018 and n = 78 in 2019).

nal model predicted probabilities of early-life LD of around 40% at 320 days, 20% at 345 days and 10% at 360 days.

The present case definition of cases which were presented to a veterinary surgeon and required some form of intervention, was chosen in order to capture the more severe presentations of LD. The follow-up period used in the present work (6 months, 180 days) was chosen to capture manifestations of LD that were most likely to be congenital in origin, whilst allowing for possible delays between clinical signs and veterinary intervention. Treatment of flexural deformities (contracture) with intravenous oxytetracycline is commonly performed in young foals in the first few days of life [5]. Therefore, these individuals may be presented to a veterinary surgeon earlier, as was the case in the present study, than those with angular deformities, which are commonly treated using remedial farriery and various techniques resulting in retardation of the growth plates undertaken when individuals are older [7]. In the Thoroughbred breeding industry, due to financial constraints and the expertise of farriers and farm personnel, it is not uncommon for on-farm management and remedial farriery to be attempted in many cases prior to seeking veterinary advice. Given that farriery intervals can be of several weeks [7], such practices could lead to substantial delays between clinical signs and veterinary intervention for some presentations of LD. The incidence of early-life LD reported in the present study (21%) is comparable to those reported for noninfectious orthopedic conditions in Thoroughbred foals in the first 48 hours [1] and first month [10] of life in previous studies. It is however interesting to note, if cases which were reported to have received remedial farriery but were not examined by a veterinary surgeon were included, it is estimated that up to 40% of the cohort may have been affected by LD [2].

It is recognized in horses, that premature foals (gestation length <320 days) are at increased risk of incomplete ossification of the small tarsal and carpal bones [29]. Although incomplete ossification was not reported in the present study population, foals with this condition most commonly present clinically with limb deformities [29]. It is therefore interesting to note that in two previous studies, the degree of ossification of foals' tarsal and carpal regions, the neonatal skeletal ossification index (NSOI), was demonstrated to be positively correlated with gestation length [30,31]. These studies had some limitations, such as small sample size [30] and evaluation of only individuals with incomplete ossification [31], however the shape of relationship described is in keeping with that demonstrated in the present work. It is therefore plausible that incomplete ossification could have existed to some extent in the present study population, in shorter gestation length individuals, but been diagnosed clinically as LD. For these reasons findings from the present study, showing a continual decrease in LD risk also within the normal gestation length period, could support the need for further evaluation of skeletal ossification in foals affected by congenital LD, rather than only in cases presenting with gestation lengths <320 days and/or clinical signs of dysmaturity as has been previously recommended [29].

In several studies, mares bred early in the breeding season were observed to have significantly longer gestation lengths, compared to those bred towards the end of the season [32–34]. It is believed that such differences arise from mares being somehow programmed to give birth in the northern hemisphere in the spring season, to ensure the most optimal conditions for survival of offspring in the wild, in terms of weather and the availability and nutritional content of pasture [35]. In the UK, additional concentrate feed is commonly provided to mares in late gestation, where it is believed that maternal overnutrition is commonplace [36]. Given seasonal differences in pasture growth and nutritional availability [37], it could be assumed that overnutrition may therefore be more likely in later-foaling mares grazing rich spring grass. Obese mares have been demonstrated to produce heavier foals [38], in which conformational defects and nonseptic neonatal orthopedic conditions are reported to be more prevalent [10]. Unfortunately, in the present study birthweight data were only available for a small number (n = 40) of individuals, and mare nutritional or body condition data were not available. However, it is interesting to note, that the incidence of LD in offspring from mares covered in June (40%), which in the context of the above may be those most likely to have both shorter gestation lengths and/or maternal overnutrition in late gestation, was double that observed in offspring from mares covered in earlier months (~20%). This highlights the importance of furthering understanding of the influence of maternal nutrition on foetal growth and development and congenital LD. It is important to acknowledge that the number in this group of late-foaling mares was low (n = 5), most likely due to reproductive management practices directed towards breeding mares as early in the year as possible, given that foals born earlier in the year are more developed at both yearling sales and at commencement of their two-year-old racing career [39]. However, until such time that

Table 2
Descriptive and univariable logistic regression analysis results of potential risk factors for early-life limb deformity (LD) in a cohort of 272 live-born foals from of 233 Thoroughbred mares on seven farms in the UK and Ireland, over two breeding seasons (n = 194 conceived in 2018 and n = 78 in 2019).

Variable	Level	n	LD *n*	% LD	95% CI (LD incidence)	OR	95% CI (OR)	Wald *P*-value	Likelihood ratio test *P*-value
Farm[a]	1	13	2	15.4	4.3–42.2	0.88	0.18–4.23	0.87	.03
(n = 272)	2	134	23	17.2	11.7–24.1	*Reference*			
	3	22	8	36.4	19.7–57.0	2.75	1.03–7.33	0.04	
	4	32	11	34.5	20.4–51.7	2.52	1.03–5.95	0.03	
	5	24	7	29.2	14.9–49.2	1.99	0.74–5.34	0.17	
	6	25	1	4.0	0.7–19.5	0.20	0.03–1.56	0.12	
	7	22	5	22.7	10.1–43.4	1.42	0.47–4.23	0.53	
Mare									
Age[b] (years)	4–5	76	12	15.8	9.3–25.6	1.03	0.96–1.11	0.37	.37
(n = 272)	6–7	74	14	18.9	11.6–29.3				
	8–10	63	16	25.4	16.3–37.3				
	>10	59	15	25.4	16.0–37.8				
No. of previous live foals[a,b]	0	55	8	14.5	7.6–26.2	1.08	0.97–1.20	0.15	.15
(n = 256)	1	44	8	18.2	9.5–32.0				
	2	47	6	12.7	5.9–25.2				
	3–4	61	20	32.8	22.3–45.3				
	>4	49	11	22.4	13.0–35.9				
No. of cycles covered[a,b] (n = 260)	1	187	42	22.5	17.1–30.0	0.68	0.39–1.20	0.19	.19
	2	56	11	19.6	11.3–31.8				
	≥3	14	1	7.1	1.3–31.5				
Status	Foaling	172	40	23.8	18.1–30.7	*Reference*			.52
(n = 272)	No live foal	49	9	18.4	9.8–31.4	0.74	0.33–1.66	0.47	
	Maiden	48	8	16.7	8.7–29.6	0.66	0.28–1.52	0.33	
Month of cover (n = 272)	Feb	35	6	17.1	8.1–32.7	*Reference*			.85
	Mar	78	16	20.5	13.0–30.7	1.24	0.44–3.51	0.67	
	Apr	104	23	21.1	15.2–31.0	1.37	0.51–3.71	0.53	
	May	48	10	20.8	11.7–34.2	1.27	0.41–3.90	0.67	
	Jun	5	2	40.0	11.8–76.9	3.22	0.44–23.65	0.25	
Pregnancy									
Gestation length[ab] (days)	314–330	17	5	29.4	13.3–53.1	0.96	0.93–0.99	0.01	.01
(n = 270)	331–360	245	48	19.6	15.1–25.0				
	361–381	21	0	0	0–15.4				
Dystocia[a]									
(n = 272)	No	256	51	19.2	15.5–25.2	*Reference*			.12
	Yes	16	6	37.5	18.5–61.4	2.41	0.84–6.94	0.12	
Sex	Colt	136	31	22.8	16.5–30.5	*Reference*			.46
(n = 272)	Filly	136	26	19.1	13.4–26.5	0.80	0.44–1.44	0.46	
Season	2019/20	194	43	22.2	16.9–28.5	*Reference*			.44
(n = 272)	2018/19	78	14	17.9	11.0–27.9	0.77	0.39–1.50	0.44	
Gestational disease, injury and medication									
Musculoskeletal disease/injury (n = 200)	No	155	35	22.6	16.7–29.9	*Reference*			.96
	Yes	45	10	22.2	12.5–36.3	0.98	0.44–2.17	0.95	
Placentitis (n = 200)	No	191	43	22.5	17.2–28.9	*Reference*			.98
	Yes	9	2	22.2	6.3–54.7	0.98	0.20–4.91	0.98	
Mastitis	No	191	42	22.0	16.7–28.4	*Reference*			.44
(n = 200)	Yes	9	3	33.3	12.1–64.6	1.77	0.42–7.39	0.44	
Antibiotic (n = 200)	No	149	36	24.2	18.0–31.6	*Reference*			.34
	Yes	51	9	17.6	9.6–30.3	0.67	0.30–1.51	0.34	
NSAID	No	154	35	22.7	16.8–30.0	*Reference*			.89
(n = 200)	Yes	46	10	21.7	12.3–35.6	0.94	0.43–2.09	0.89	
Altrenogest (n = 200)	No	170	39	22.9	17.3–29.8	*Reference*			.72
	Yes	30	6	20.0	9.5–37.3	0.84	0.32–2.20	0.72	
Sedative	No	187	43	23.0	17.5–29.5	*Reference*			.53
(n = 200)	Yes	13	2	15.4	4.3–42.2	0.61	0.13–2.85	0.53	

Abbreviations: CI = confidence interval; No. = number; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio.
[a] Univariable $P < .20$ and variable taken forward for consideration for inclusion into multivariable model.
[b] Mare age, number of previous live foals, number of cycles covered, and gestation length were modelled as continuous variables but grouped into categories to illustrate LD incidence in progeny from each category; the number of pregnancies for which complete data were available are given in brackets (n) below each exposure variable.

the underlying mechanisms behind any such associations are fully understood, breeding mares early in the season may offer some protective effect in terms of the risk of LD in foals.

Both maternal disease and medication usage during pregnancy have the potential to affect foetal growth and development [40], which is why associations between such exposures and LD were investigated in the present study. Placentitis, for example, is well recognized in horses as having the potential to lead to in-utero growth retardation, premature parturition and low birthweight [41,42]. In terms of medications, phenylbutazone, one of the most commonly utilized medications in the present population (23% [26]), has not undergone definitive safety studies during pregnancy in horses [43], despite fetotoxic effects having been reported in experimental animal models [44]. Although no associations were found between the gestational disease and medication exposures investigated in the present work and early-life LD, it must be acknowledged that only a limited number were investigated, and lack of data availability for all pregnancies and low case numbers for some conditions may have affected study power. Given the frequency of gestational disease and injury (34%) and medication usage (47%) reported in this study population [26], further work is required to evaluate associations between disease, injury and medication usage in Thoroughbred broodmares and offspring health outcomes.

The main limitations of this work were the retrospective nature of the mare and pregnancy data, which were not collected specifically for the purposes of this study, and the relatively small sample size which, as previously discussed, may have affected the statistical power of the study. Farms were self-selected as those willing to prospectively collect data for the foals enrolled in the birth cohort over a lengthy study period, which could affect the generalizability of the findings. The use of veterinary records to identify early-life LD in foals could have underestimated the true incidence of LD in the population, as some cases may be managed on-farm without veterinary intervention.

5. Conclusions

There is evidence to suggest that, also within the normal range of gestation length for Thoroughbred foals, longer gestation lengths may be associated with reduced risk of early-life LD. Further work is however required to elucidate the biological mechanisms behind this relationship. In the meantime, management strategies to breed Thoroughbreds early in the year may, via seasonal differences in gestation lengths and maternal nutrition, have the potential to offer some protective effect.

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Declaration of Competing Interest

None.

CRediT authorship contribution statement

Rebecca Mouncey: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Juan Carlos Arango-Sabogal:** Formal analysis, Writing – review & editing. **Amanda M. de Mestre:** Conceptualization, Writing – review & editing, Funding acquisition. **Kristien Verheyen:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jevs.2023.104896.

References

[1] Raidal SL, Hughes KJ, Eastwell B, Noble N, Lievart J. Prevalence and performance effects of neonatal disease in Thoroughbred and Standardbred foals in South-Eastern Australia. Aust Vet J 2021;99:152–62. doi:10.1111/avj.13056.
[2] Mouncey R, Arango-Sabogal JC, de Mestre AM, Verheyen KL. Incidence of disease, injury and death in Thoroughbred foals and yearlings on stud farms in the UK and Ireland. Vet Rec 2023;e2994. doi:10.1002/vetr.2994.
[3] Mouncey R, Arango-Sabogal JC, de Mestre AM, Verheyen KL. Retrospective analysis of post-mortem findings in Thoroughbreds aged from birth to 18 months presented to a UK pathology laboratory. Vet J 2022;e105813. doi:10.1016/j.tvjl.2022.105813.
[4] Galvin N, Corley K. Causes of disease and death from birth to 12 months of age in the Thoroughbred horse in Ireland. Ir Vet J 2010;63(1):37–43. doi:10.1186/2046-0481-63-1-37.
[5] Kidd J. Flexural deformities part 1: congenital. In Pract 2017;39(3):128–34. doi:10.1136/inp.j172.
[6] Gaughan EM. Flexural limb deformities of the carpus and fetlock in foals. Vet Clin North Am Equine Pract 2017;33(2):331–42. doi:10.1016/j.cveq.2017.03.004.
[7] Witte S, Hunt R. A review of angular limb deformities. Equine Vet Educ 2009;21(7):378–87. doi:10.2746/095777309X440096.
[8] O'Donohue DD, Smith FH, Strickland KL. The incidence of abnormal limb development in the Irish thoroughbred from birth to 18 months. Equine Vet J 1992;24(4):305–9. doi:10.1111/j.2042-3306.1992.tb02841.x.
[9] Price Waterhouse Cooper. Economic impact study of Britain's thoroughbred breeding in 2023. Available from: https://www.thetba.co.uk/asset/A8F0D1D1-C908-4767-9BF3ED846785D9DC/Accessed April 2023.
[10] Whittaker S, Sullivan S, Auen S, Parkin TDH, Marr CM. The impact of birthweight on mare health and reproductive efficiency, and foal health and subsequent racing performance. Equine Vet J 2012;44(41):26–9. doi:10.1111/j.2042-3306.2011.00479.x.
[11] Elliott C, Morton J, Chopin J. Factors affecting foal birth weight in Thoroughbred horses. Theriogenology 2009;71(4):683–9. doi:10.1016/j.theriogenology.2008.09.041.
[12] Hendriks WK, Colenbrander B, van der Weijden GC, Stout TAE. Maternal age and parity influence ultrasonographic measurements of fetal growth in Dutch Warmblood mares. Anim Reprod Sci 2009;115(1):110–23. doi:10.1016/j.anireprosci.2008.12.014.
[13] Klewitz J, Struebing Rohn K, Goergens A, Martinsson G, Orgies F, et al. Effects of age, parity, and pregnancy abnormalities on foal birth weight and uterine blood flow in the mare. Theriogenology 2015;83(4):721–9. doi:10.1016/j.theriogenology.2014.11.007.
[14] Scoggin CF. Not just a number: effect of age on fertility, pregnancy and offspring vigour in thoroughbred brood-mares. Reprod Fertil Devel 2015;27(6):872–9. doi:10.1071/RD14390.
[15] Meirelles MG, Veras MM, Alonso MA, de Fátima Guimarães C, Nichi M, Fernandes CB, et al. Influence of maternal age and parity on placental structure and foal characteristics from birth up to 2 years of age. J Equine Vet Sci 2017;56:68–79. doi:10.1016/j.jevs.2017.03.226.
[16] Robles M, Dubois C, Gautier C, Dahirel M, Guenon I, Bouraima-Lelong H, et al. Maternal parity affects placental development, growth and metabolism of foals until 1 year and a half. Theriogenology 2018;108:321–30. doi:10.1016/j.theriogenology.2017.12.019.
[17] Weatherbys Bloodstock Publications. Return of mares 2018-2020. Supplement to volumes 45-47 of the general stud book. Bloodstock Publications—Weatherbys Shop.
[18] Racing Post. Bloodstock. Wellingborough, UK. Available at: https://ww.racingpost.com/bloodstock Accessed July 2019.
[19] Frazer GS, Embertson RM, Perkins NR. Complications of late gestation in the mare. Equine Vet Educ 2002;14(5):16–21. doi:10.1111/j.2042-3292.2002.tb01789.x.
[20] LeBlanc MM. Common peripartum problems in the mare. J Equine Vet Sci 2008;28:709–15. doi:10.1016/j.jevs.2008.10.007.
[21] Johnson PJ, Messer NT, Ganjam SK, Weidmeyer CE. Pregnancy-associated laminitis in mares. J Equine Vet Sci 2009;29:42–6. doi:10.1016/j.jevs.2008.11.009.
[22] Tilbary A, Pearson LK. Mare problems in the last month of pregnancy. Proc Am Assoc Equine Practitioners 2012;58:350–8.
[23] Bishop Y. The Veterinary Formulary. 4th ed. London: Pharmaceutical Press; 1998.
[24] Dohoo I, Martin W, Stryhn H. Introduction to clustered data. In: Veterinary Epidemiologic Research. VER Inc; 2014. p. 535.
[25] StataCorp., Margins—Marginal means, predictive margins, and marginal effects. StataCorp, LLC College Stations TX: https://www.stata.com/manuals/rmargins.pdf. p. 1-58.
[26] Mouncey R, Arango-Sabogal JC, de Mestre AM, Verheyen KL. Descriptive study of medication usage and occurrence of disease and injury during gestation in Thoroughbred broodmares. J Equine Vet Sci 2022;118:104104. doi:10.1016/j.jevs.2022.104104.
[27] Clothier J, Hinch G, Brown W, Small A. Equine gestational length and location: is there more that the research could be telling us? Aust Vet J 2017;95(12):454–61. doi:10.1111/avj.12653.
[28] Rossdale PD. A clinician's view of prematurity and dysmaturity in thoroughbred foals. Proc R Soc Med 1976;69(9):631–2 PMC1864628.

[29] McIlwraith CW. Incomplete ossification of carpal and tarsal bones in foals. Equine Vet Educ 2003;15(2):79–81. doi:10.1111/j.2042-3292.2003.tb00220.x.
[30] Adams R, Poulos P. A skeletal ossification index for neonatal foals. Vet Radiol 1988;29(5):217–22. doi:10.1111/j.1740-8261.1988.tb01503.x.
[31] Haywood L, Spike-Pierce DL, Barr B, Mathys D, Mollenkopf D. Gestation length and racing performance in 115 Thoroughbred foals with incomplete tarsal ossification. Equine Vet J 2018;50:29–33. doi:10.1111/evj.12712.
[32] Marteniuk JV, Carleton CL, Lloyd JW, Shea ME. Association of sex of fetus, sire, month of conception, or year of foaling with duration of gestation in Standardbred mares. J Am Vet Med Assoc 1998;212:1743–5 PMID: 9621882.
[33] Pérez CC, Rodríguez I, Mota J, Dorado J, Hidalgo M, Felipe M, et al. Gestation length in Carthusian Spanishbred mares. Livest Prod Sci 2003;82:181–7. doi:10.1016/S0301-6226(03)00027-7.
[34] Ewert M, Lüders I, Böröcz J, Uphaus H, Distl O. Determinants of gestation length in Thoroughbred mares on German stud farms. Anim Reprod Sci 2018;191:22–33. doi:10.1016/j.anireprosci.2018.02.001.
[35] Bronson FH, Heideman PD. Seasonal regulation of reproduction in mammals. In: Knobil E, Neill JD, editors. The Physiology of Reproduction. New York: Raven Press; 1994. p. 541–84.
[36] Coverdale JA, Hammer CJ, Walter KW. Horse species symposium: nutritional programming and the impact on mare and foal performance. J Anim Sci 2015;93(7):3261–7. doi:10.2527/jas.2015-9057.
[37] Mitchell B. The nutritional contribution of grass to the equine diet. Equine Health 2017(35):14–17. doi:10.12968/eqhe.2017.35.14.
[38] Smith S, Marr CM, Dunnett C, Menzie-Gow NJ. The effect of mare obesity and endocrine function on foal birthweight in Thoroughbreds. Equine Vet J 2017;49(4):461–6. doi:10.1111/evj.12645.
[39] Arango-Sabogal JC, Mouncey R, de Mestre AM, Verheyen KL. Date of birth and purchase price as foals or yearlings are associated with Thoroughbred flat race performance in the United Kingdom and Ireland. Vet Rec Open 2022;9(1):e43. doi:10.1002/vro2.43.
[40] Fowden AL, Giussani DA, Forhead AJ. Physiological development of the equine fetus during late gestation. Equine Vet J 2020;52(2):165–73. doi:10.1111/evj.13206.
[41] Canisso IB, Ball BA, Squires EL, Troedesson MHT. Comprehensive review on equine placentitis. AAEP Proceedings 2015;61:490–509.
[42] Foote AK, Rickets SW, Whitwell KE. A racing start in life? The hurdles of equine feto-placental pathology. Equine Vet J 2012;44(41):120–9. doi:10.1111/j.2042-3306.2011.00507.x.
[43] National Office of Animal Health. Compendium of data sheets for animal medicines 2020. Available from: https://www.noahcompendium.co.uk/?id=-449662 Accessed August 2022.
[44] Combes RD. Is Phenylbutazone a genotoxic carcinogen? A weight-of-evidence assessment. Altern Lab Anim 2013;41:235–48. doi:10.1177/026119291304100307.