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Differential impact of birth weight and early growth on neonatal mortality in puppies[1,2]

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ABSTRACT: Breeding kennels face a high rate of neonatal mortality, on which the impact of nutrition remains to be determined. This study was designed to evaluate the impact of birth weight (reflecting intrauterine growth) and early growth rate (reflecting colostrum intake) on risk of neonatal mortality in puppies and to determine the critical thresholds of both parameters. Puppies from various breeds were weighed at birth ($n = 514$) and at 2 d of age, and the growth rate over that period (early growth rate) was calculated for all survivors ($n = 477$). Linear mixed models evaluated the effect of birth weight on mortality between birth and 2 d of age and the effect of both birth weight and early growth rate on mortality between 2 and 21 d of age. Birth weight was influenced by litter size ($P = 0.003$), with more low-birth-weight puppies (the lightest 25% within a breed size) in large litters compared with smaller litters. Mortality over the first 2 d after birth was associated with birth weight ($P < 0.001$), with 81.1% of dying puppies characterized by a low birth weight. Mortality between 2 and 21 d of age was not related to birth weight but was found to be associated with early growth rate ($P < 0.001$), with higher risk of death in puppies with growth rate at or below –4% after the first 2 d of life. This study demonstrates the differential effect of intrauterine nutrition impacting mortality during the first 2 d of life and that of colostrum intake impacting mortality until 21 d of life. Birth weight and early growth rate thresholds provided in this study allow identification of puppies at risk, whereby provision can be made for adequate nursing to increase their chances to survive.

Key words: birth weight, colostrum intake, litter size, mortality, puppy, weight change

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INTRODUCTION

Prevalence of mortality during the first 3 wk after birth in the canine species is one of the highest among domestic animals: around 17% of puppies die during this perinatal period (stillbirth and neonatal mortality; Potkay and Bacher, 1977; Gill, 2001; Nielen et al., 2001; Indrebø et al., 2007). Mortality risk first depends on intrauterine growth, with puppies of the lowest weight at birth being at higher risk of neonatal death compared with littermates (Grundy, 2006), as observed in kittens and piglets (Lawler, 2008; Devillers et al., 2011). In large-sized breeds, puppies dying during the first week after birth had over 100 g lower birth weight than puppies still alive at 8 wk (Indrebø et al., 2007). However, birth weight thresholds for the different breed sizes defining puppies at risk of death, requiring more intensive nursing, as well as factors impacting birth weight are not defined to date.

After birth, at an early stage of life, canine newborns depend entirely on colostrum intake. This specific mammary secretion provides puppies with not

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only nutrients but also hormones, growth factors, and passive immunity. All of mentioned components are indispensable for the puppy's life, as hypoglycemia and hypothermia, together with infectious diseases, are recognized as the major causes of neonatal mortality in puppies (Indrebø et al., 2007; Münnich and Küchenmeister, 2014). Whereas energy intake covers the basal metabolic needs, ensuring thermoregulation and body growth, immunoglobulin acquisition early after birth provides the only immune protection during the first weeks. In piglets, early weight gain is used to evaluate the amount of colostrum ingested and eventual risk of neonatal death, as piglets dying before weaning gained less weight between birth and 24 h of life (Devillers et al., 2011). Although a 10% loss of birth weight is commonly considered to be physiological in 2-d-old puppies (Grundy, 2006), the real impact of early weight change on canine neonatal mortality is unknown.

The aim of this study was to evaluate the relationship between neonatal mortality in puppies and both birth weight and growth rate during the first 2 d of life (early growth rate). The critical thresholds of birth weight and early growth rate defining puppies at higher risk of death were also determined.

Table 1. Breed size classification according to the adult BW and numbers of litters and puppies included in the study

Breed size	Breed	Number of litters born	Number of live-born puppies
Small, <15 kg	Bichon Frise	4	15
	Bichon Maltese	7	40
	Jack Russell Terrier	4	12
	Lhasa Apso	11	50
	Pomeranian	1	4
	Poodle	8	28
	Shih Tzu	6	32
	German Spitz	3	11
	Scottish Terrier	1	1
	West Highland White Terrier	7	35
	Yorkshire Terrier	2	15
Medium, 15–25 kg	Cocker Spaniel	17	90
Large, >25 kg	Boxer	1	8
	Labrador	11	58
	German Shepherd	2	11
	Golden Retriever	15	104
Total		100	514

MATERIALS AND METHODS

The protocol was reviewed and approved by the Royal Canin Internal Ethics Committee (AF/20140704).

Study Population

The experiment was performed on all puppies born alive from 100 bitches within 1 breeding kennel. Ninety-eight bitches were multiparous. Between 1 wk before parturition and the end of lactation, bitches were housed in a single box (2–4 m^2) and fed a dry balanced diet for growing dogs (Starter; Royal Canin, Aimargues, France) ad libitum. Whelping boxes were heated (continuous under floor heating plus a heat infrared lamp during the first 3–5 d after whelping), so that the stable temperature of 28 to 30°C at the ground level was assured. None of the whelpings were assisted, no cesarean section was performed, and no puppies were hand reared during the experiment. After whelping, the total number of puppies born within a litter (born alive or dead [stillborn]), defining litter size, was recorded. Each puppy was identified by a colored woolen collar and its sex, breed, and the age of its dam were recorded. Within the first 8 h after birth, puppies were weighed using a calibrated analytical scale in 1-g increments (Fisher Scientific International Inc., Hampton, NH). At 48 h of life, mortality was registered and all surviving puppies were weighed again. Their growth rate over the first 2 d of life was calculated [(weight at 2 d – weight at birth)/weight at birth × 100%]. Mortality between 2 and 21 d was then registered.

Statistical Analyses

Statistical analyses were performed with the Statistical Analysis Systems statistical software package version 9.3 (SAS Inst. Inc., Cary, NC). The normality was evaluated with the Shapiro–Wilk test. Univariable statistical analyses were performed with the Kruskal–Wallis test.

Dams were classified into young (≤6 yr of age) and old (>6 yr of age). Depending on adult weight, neonates and their dams were classified into small breed dogs (<15 kg), medium breed dogs (15–25 kg), and large breed dogs (>25 kg; Table 1). Because birth weight and litter size vary among breeds (Grundy, 2006), birth weight and litter size values were classified into quartiles, separately, for small, medium, and large breed puppies (Table 2). The first quartile (**Q1**) represents the lowest 25% of registered values, the second and third quartiles (**Q2** and **Q3**, respectively) represent 25% of values below and above the median, and fourth quartile (**Q4**) represents the highest 25% of registered values.

First, a generalized linear mixed model (GLIMMIX procedure) with birth weight as an outcome (trans-

Table 2. Classification of puppies according to birth weight and litter size (514 puppies) depending on breed size

Breed size	Number of puppies	Median birth weight, g	Quartiles of birth weight,[1] g				Median litter size	Quartiles of litter size, number of puppies per litter			
			Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4
Small	243	185[a]	<151	151–185	186–219	>219	4[a]	<4	4	5	>5
Medium	90	267[b]	<225	225–267	268–309	>309	5[b]	<5	5	6	>6
Large	181	377[c]	<330	330–377	378–428	>428	7[c]	<6	6–7	8–9	>9

[a–c]Median values within a column with different superscripts were significantly different ($P < 0.05$).

[1]Q1 = lowest 25% registered values; Q2 = 25% of values below the median; Q3 = 25% of values above the median; Q4 = highest 25% registered values.

formation in ordinal outcome) was used to assess the following fixed effects: sex of the puppy (male or female), litter size, and age of the dam (young or old). Subsequently, a GLIMMIX procedure with mortality between birth and 2 d of age as a binary outcome (logit transformation) was used to assess the following fixed effects: sex of the puppy, litter size, age of the dam, breed size, and birth weight.

Second, a linear mixed model (MIXED procedure) was performed to determine the variables affecting growth rate between birth and 2 d of age. As residuals of this multivariable model were not normally distributed, a nonparametric analysis was performed (rank transformation of the outcome). This model included, as fixed effects, sex, litter size, age of the dam, breed size (small, medium, or large), and birth weight. Subsequently, a GLIMMIX procedure with mortality between 2 and 21 d of age as a binary outcome (logit transformation) was used to assess the following fixed effects: sex, litter size, age of the dam, breed size, and birth weight. Moreover, the effect of growth rate was added as a covariate. In all multivariable models, litter was modeled as a random effect.

A receiver operating characteristic curve was drawn based on the result of the logistic model on mortality between 2 and 21 d of age. The Hosmer and Lemeshow goodness-of-fit test permitted assessment of the quality of this model. The best cutoff from the model for high and low mortality risk populations was defined based on Youden's index. Differences were considered significant at $P < 0.05$. Quantitative data are presented as medians with interquartile range (**IQR**).

RESULTS

The median age of the 100 bitches included in the study was 6 yr (IQR: 4 to 7 yr) and median number of puppies born per litter (litter size) was 5 (IQR: 4 to 7). From a total of 532 puppies born, 18 were stillborn (3.4%). The sex ratio in 514 puppies born alive was 1.2 (280 males and 234 females). Birth weight varied from 80 to 604 g. Both birth weight and litter size were significantly different between small, medium, and large breeds ($P < 0.001$ in both models; Table 2). Weight at birth was significantly influenced by litter size ($P = 0.003$) and litter effect ($P < 0.001$; Fig. 1). Among all puppies belonging to large litters (quartile 4), 37.1% (36/97) were of low birth weight (quartile 1) and 12.4% (12/97) of high birth weight (quartile 4), whereas proportions in small-sized litters (quartile 1) were 8.6% (7/81) of low birth weight and 50.6% (41/81) of high birth weight puppies. None of the other factors tested in this model (sex of the puppy and age of the dam) has any influence on puppy birth weight.

A total of 20.6% (106/514) of live-born puppies died between birth and 21 d of age, with 34.9% (37/106) of deaths occurring during the first 2 d after birth. Mortality between birth and 2 d of age was influenced by birth weight ($P < 0.001$; Table 3; Fig. 2) and tended to be influenced by breed size and litter effect ($P = 0.09$ and $P = 0.06$, respectively). Among all puppies dying within the first 48 h after birth, 81.1% (30/37) were of low birth weight (quartile 1). None of the other factors tested (such as litter size, sex of the puppy, or age of the dam) had any influence on mortality between birth and 2 d of age.

Median growth rate during the first 48 h of life calculated for 477 puppies still alive at Day 2 was 3.3%

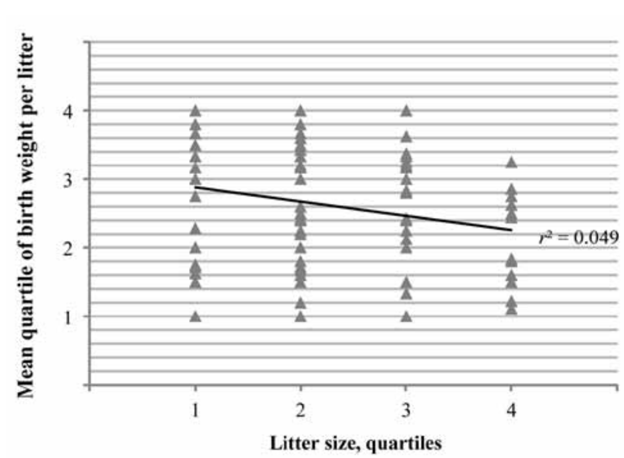

Figure 1. Correlation between litter size and mean quartile of birth weights in puppies from 1 given litter (100 litters and 514 puppies). Both variables are expressed in quartiles according to Table 2.

Table 3. Predictive factors for neonatal mortality in puppies (514 puppies; 100 litters)

	Mortality 0–2 d			Mortality 2–21 d		
Factor	*P*-value	OR[1]	95% CI[2]	*P*-value	OR	95% CI
Age of dam	0.15	0.5	0.2, 1.3	0.68	0.8	0.3, 2.3
Breed size	0.09			0.25		
Small		1.0[3]	–[4]		1.0[3]	–
Medium		0.6	0.1, 2.4		0.3	0.1, 1.3
Large		0.3	0.1, 0.9		1.1	0.4, 2.9
Sex	0.75	1.14	0.5, 2.6	0.75	0.9	0.4, 1.8
Litter size[5]	0.65			0.50		
Q1		1.0[3]	–		1.0[3]	–
Q2		0.6	0.1, 2.6		1.0	0.2, 4.0
Q3		0.4	0.1, 1.8		0.5	0.1, 1.7
Q4		0.5	0.1, 2.6		0.6	0.1, 2.8
Birth weight	<0.001			0.53		
Q1		1.0[3]	–		1.0[3]	–
Q2		22.7	5.0, 102.9		1.0	0.4, 2.5
Q3		59.4	7.3, 481.5		1.4	0.5, 4.0
Q4		16.4	4.7, 57.3		2.1	0.7, 6.7
Growth rate 0–2 d	–	–	–	<0.001	0.9	0.8, 0.9
Litter effect	0.06	–	–	<0.001	–	–

[1]OR = odd ratio.

[2]CI = confidence interval.

[3]Reference category.

[4]– = data not available.

[5]Q1 = lowest 25% registered values; Q2 = 25% of values below the median; Q3 = 25% of values above the median; Q4 = highest 25% registered values.

(IQR: –4.9 to 13.2%). No influence of birth weight on early growth rate was evidenced (Fig. 3). No effect of breed size, litter size, age of the dam, or sex of the puppy was observed on growth rate, but an effect of litter was evidenced as a random term ($P < 0.001$).

Mortality rate between 2 and 21 d of age was influenced by growth rate within the first 2 d of life and litter effect ($P < 0.001$ and $P < 0.001$, respectively; Table 3; Fig. 4). Median growth rate in puppies dying between 2 and 21 d of age was –11.3% (IQR: –16.7 to –4%) compared with 5.1% (IQR: –2.2 to 13.2%) in puppies still alive at Day 21. The optimal cutoff value of growth rate within the first 48 h of life to assess predictive likelihood of mortality between 2 and 21 d of age was –4% with a sensitivity of 75.4% and specificity of 79.7%. Among all puppies that survived until Day 2, 28.3% (135/477) had an early growth rate below or equal to –4%. Mortality rate was 38.5% (52/135) for puppies with early growth rate below this threshold vs. 5.0% (17/342) for puppies with higher growth rate values ($P < 0.001$). Neither an effect of the birth weight on mortality between 2 and 21 d of age nor of any other

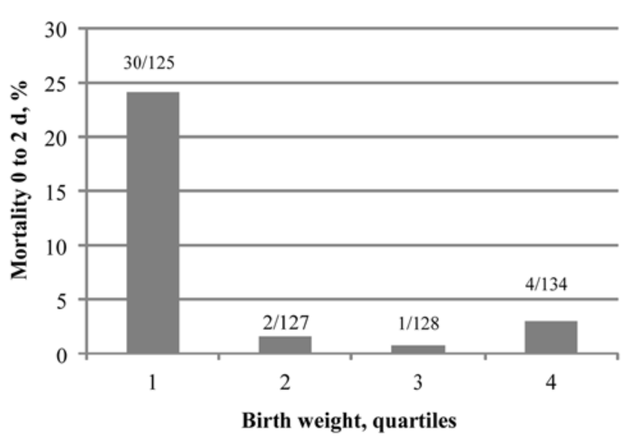

Figure 2. Relationship between mortality from birth until 2 d of age and birth weight (observations for 514 puppies; $P < 0.001$). Birth weight is expressed in quartiles as defined in Table 2.

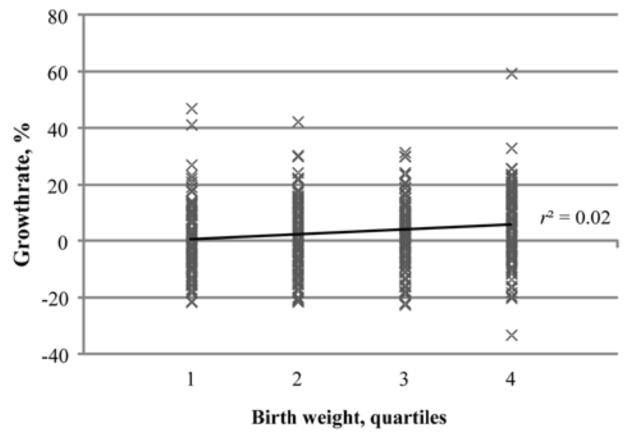

Figure 3. Relationship between birth weight and growth rate after the first 2 d of life (observations for 477 puppies; $P = 0.20$). Birth weight is expressed in quartiles as defined in Table 2. Growth rate is defined as (weight at 2 d – weight at birth)/weight at birth × 100%.

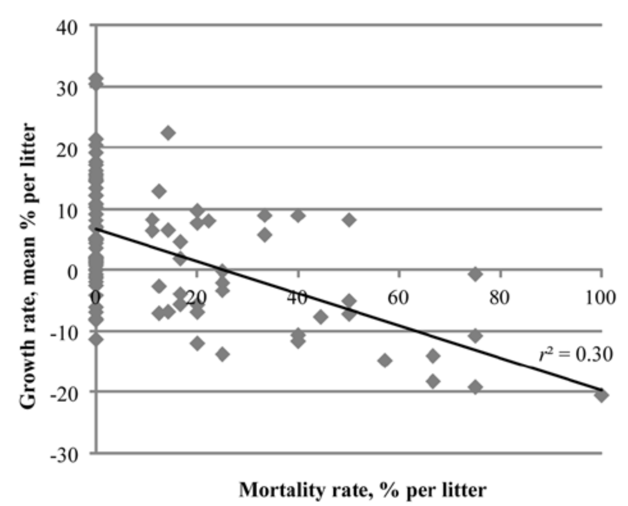

Figure 4. Correlation between early growth and neonatal mortality at a litter level (observations for 100 litters; $P < 0.001$). Early growth is expressed as the mean growth rate in puppies between 0 and 2 d of life from 1 litter. Mortality rate is the proportion of puppies dying between 2 and 21 d of age within 1 litter.

factor tested in that model (breed size, litter size, sex of the puppy, or age of the dam) was evidenced.

DISCUSSION

Canine neonates are born with very low body fat content (1.3% of the body; Kienzle et al., 1998) with most energy being provided by glycogenolysis. The decline in muscle and liver glycogen concentrations after birth is rapid (Kliegman and Morton, 1987), and gluconeogenesis is very limited due to immature liver (Miettinen and Kliegman, 1983). In parallel, shivering thermogenesis is absent up to 6 d (Münnich and Küchenmeister, 2014), which, taken together, make newborn puppies susceptible to hypoglycemia and hypothermia and, as a consequence, death. The total perinatal mortality (stillbirths and mortality during the first 3 wk of age) in our study was 23.3%, with over one-third of live-born puppies dying during the first 2 d after birth. This mortality rate is higher than those reported in other studies, ranging between 13.6 and 20.2% (Potkay and Bacher, 1977; Gill, 2001; Nielen et al., 2001; Indrebø et al., 2007). No additional nursing or hand rearing was performed in the present study, which could explain a higher mortality rate. The majority of the puppies (81.1%) dying within the first 48 h after birth were characterized by a low birth weight, previously showed in newborn infants and piglets as a risk factor for hypoglycemia and hypothermia (Williams, 1997; Laptook and Watkinson, 2008; Devillers et al., 2011). Low-birth-weight puppies, with a higher ratio between body surface and body mass than littermates, have a decreased ability to maintain stable blood glucose concentration and body temperature as well as lower ability to suckle. These factors, taken together, increase their risk of neonatal death (Grundy, 2006).

In our study, birth weight was negatively affected by litter size. A similar effect has been demonstrated in kittens, in which each additional kitten in a litter decreased mean BW by 2.2 g (mean kitten birth weight = 100 g; Sparkes et al., 2006; Gatel et al., 2011). No effect of dam age or parity has been shown in kittens or in the puppies in our study, although in foals, birth weight increases by 0.5 kg for every extra year of age of the mare (Elliott et al., 2009). Other effects common for all puppies coming from 1 litter (litter effect) had an impact on the puppy's birth weight in our study. In pigs, intrauterine growth retardation, associated with reduced birth weight, is caused not by a limited uterine space but by a smaller size of placenta and so limited transport of inter alia AA from dam to the fetus (Ashworth et al., 2001). In women, fetal growth retardation is due to insufficient concentration of nutrients in the dam's bloodstream and due to maternal vascular diseases in as many as 35% of the cases (Howie, 1982). To date, the impact of canine placental disorders on birth weight in puppies remains unknown.

To identify puppies at higher risk of death due to a low birth weight, a cutoff value has to be defined differentially according to breed size, because this factor determines weight at birth. Low birth weight values for small-, medium-, and large-sized dogs were provided in this study (Table 2), defined by the 25% owest birth weights, as puppies from the first quartile . Such puppies were proven to be at significantly higher risk of death. However, birth weights vary not only between different breed sizes (Grundy, 2006; our study) but also between breeds of the same size (Trangerud et al., 2007). Therefore, building a multibreed database with puppies' birth weights and their mortality could lead to an even better estimate of the chances of a just born puppy to survive and to provide it an adequate care if needed.

In contrast to a dramatic impact on mortality within the first 2 d after birth, birth weight was not associated with mortality between 2 and 21 d of age. A major risk factor for mortality during that period was growth rate during the first 2 d of life. This relationship could be explained by colostrum intake and the nutritional and/or immunological value of the colostrum (GE at Day 1 of lactation: 548 kJ/100 g [unpublished data]; IgG: 19.4 g/L [Mila et al., 2014]). Due to the endotheliochorial placenta, the transfer of immunoglobulins from dam to fetus is very limited in dogs. Puppies acquire 90% of their passive immunity via colostrum ingested within the first 12 to 16 h of life (Chastant-Maillard et al., 2012). Indeed, serum IgG concentration at 2 d of age (as a marker of passive immune transfer) has been demonstrated to be strongly associated with growth rate within the first 2 d of life as well as with neonatal mortality. Over 44% of puppies with an IgG concentration at Day 2 at or below 2.3 g/L, defined as passive immune deficit in dogs, died during the neonatal period compared with only 5% in puppies with higher IgG concentrations (Mila et al., 2014).

Energy provided by the colostrum can also explain the link between early growth and neonatal mortality. In 2-d-old piglets, colostrum intake, evaluated through weight gain after the first 24 h of life, was positively associated with rectal temperature and glucose concentration, showing the important role of colostrum in thermoregulation and glucose homeostasis (Devillers et al., 2011). The ability to maintain stable body temperature as well as blood glucose level is very limited in canine newborns, and hypothermia and hypoglycemia may have fatal consequences for puppies (Münnich and Küchenmeister, 2014). The early growth rate threshold, below which risk of mortality is significantly increased, was calculated at or below –4% in this study. Weight monitoring, together with the cutoff value calculated in our study, provide an easy tool to detect and nurse puppies at increased risk of hypoglycemia or hypothermia and, by consequence, risk of neonatal mortality.

The positive effect of colostrum on survival might be also related to its bioactive compounds, such as prolactin, steroids, insulin, leptin, and many growth factors, essential for correct organ development and maturation (Hamosh, 2001; Farmer et al., 2006). Amino acids together with Insulin-like Growth Factors, highly concentrated in swine colostrum (Donovan et al., 1994), have a stimulatory effect on protein synthesis in the piglet intestinal tract 50-fold stronger than mature milk (Burrin et al., 1992). In puppies, a large increase in intestinal dimensions (i.e., 42% in mucosal weight) occurs within the first 24 h of life, dramatically improving food intake, digestion, and nutrients absorption (Paulsen et al., 2003). Insufficient colostrum intake, as evidenced by reduced growth over the first 2 d of life, may, therefore, reduce nutrient absorption later in life, leading to higher mortality rates in puppies.

Although differences in postweaning growth curves and adult weights between females and males have been demonstrated in dogs (Helmink et al., 2000) and in cats (Moik and Kienzle, 2011), no sexual dimorphism in birth weights or early growth was evidenced in our study. Interestingly, growth during the first 2 d of life was not found to be associated with birth weight, whereas in many other species an accelerated growth occurs, compensating the lower weight at birth (Binkin et al., 1988; Moik and Kienzle, 2011). In rabbits and rats, litter size, negatively correlated with pup growth, explains most of the preweaning growth variation (Rödel et al., 2008). In our study, not litter size but litter effect as a random term for all littermates had an influence on early growth rate. Insufficient milk yield, as shown previously in pigs (Marshall et al., 2006), together with poor maternal behavior and other circumstances precluding colostrum intake, could be responsible for decreased growth in some litters.

Conclusions

This study illustrates the differential impact of birth weight and early growth rate on neonatal mortality, either mortality during the first 2 d after birth or mortality between 2 d and 3 wk of age. It also provides critical thresholds allowing identification of puppies with particular need of monitoring and nursing during the neonatal period. However, these values remain to be refined for various dog breeds as well as different kennels. This study highlights the need for further investigation on intrauterine growth (to decrease the incidence of low birth weights) and on colostrum intake (to optimize early growth) to reduce the high incidence of neonatal mortality in the canine species.

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