

## Canine neonatology: prediction of puppy survival

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In canine newborns, the process of neonatal adaptation to the extra uterine life is considered less efficient compared to other domestic species, and consequently, the multisystemic immaturity that persists during the neonatal period puts the newborn puppies at a high vulnerability increasing the risk of mortality.

Many factors can contribute to canine perinatal mortality, including parental genetics, maternal factors, environmental factors, and puppy factors, which can be often related to each other<sup>1</sup>.

The perinatal mortality, considered as the sum of stillbirth plus deaths occurring during the neonatal period, meaning the first 3-4 weeks after birth, can reach values as high as 10-30%, with about 65% of deaths occurring during the first week of age, with a high percentage of deaths due to stillbirth<sup>2</sup>.

Although canine perinatal death can be addressed to a plethora of causes, in most cases, the underlying cause can be related to the process of birth and factors disturbing the neonatal adaptation, affecting the possibility of survival in the short-, but also in the long-term.

The availability of tools able to predict the survival of each newborn could be beneficial to avoid losing time and effort behind a puppy with a high probability of dying, allowing focused assistance to those newborns with better chances of survival. This aspect, reported to be important in human neonatology, becomes even more important in canine neonatology, in which multiple neonates must be evaluated and, if needed, assisted, at each parturition.

Neonatal adaptation, the absolute prerequisite for newborn survival, is a complex process in which many physiologic changes must occur in the correct sequence, timing, and intensity in a well-prepared, at term, fetus at birth. The first and most important change is the beginning of efficient respiration soon after birth which allows the functionality of the cardio-circulatory system and allows a cascade of other vital physiological changes such as a plethora of neurologic functions, the gastro-intestinal and kidney function, etc. The efficiency of neonatal adaptation lies upon a puzzle of factors, involving fetal maturity, newborn viability, newborn metabolic efficiency, birth weight, and the absence of life-threatening malformations or physical defects.

Although some aspects are still not completely investigated and known, in the last decades the scientific interest in canine neonatology has led to an increasing knowledge about the normal canine newborn and about the possibility of predicting puppy survival in the short- and long-term, by evaluation of some clinical or laboratory parameters.

From a clinical standpoint, evaluation of maturity, viability, absence of malformations, birth weight (BW), and body temperature are cornerstones for predicting newborn survival/mortality. Regarding laboratory analysis, the most useful are related to the assessment of asphyxia and consequent acidosis, hypo- and hyperglycemia, and passive immune transfer.

Recognizing the utmost importance of fetal maturity, little is still known about assessing the canine readiness for birth, except for detecting very premature births<sup>3</sup>. Likely, the impact of underdeveloped newborns, in cases of small for gestational age newborns and/or intrauterine growth restriction, remains unclear in the dog. However, the importance of correct BW and the constant weight gain during the neonatal period is well known and represents key factors for prediction of puppy survival. Birth weight results from an adequate intrauterine environment, placental function and efficiency, fetal development and growth, and the importance of neonatal- maternal body weight ratio at birth as a prognostic factor for the puppy has been reported<sup>4</sup>. Due to the wide range of body sizes among canine breeds, studies are focussing on providing BW reference values and growth curves specific for breeds, or at least grouped according to breed body 53

size. Due to the important role of BW, the concepts of low BW (LBW) and very low BW (VLBW) have been investigated, providing important and useful information about the relationship between BW deficit and survival prognosis. Not only the BW but also the loss of weight in the first 4 days after birth and the lack of weight gain after birth, have been related to puppies' death within the first 3 weeks of age<sup>9,15-17</sup>.

Many studies have focussed on the evaluation of newborn dog viability at birth. Viability is considered the physiologic condition and reactivity of a neonate that influences the chance of survival and is largely recognized as a key factor in newborn adaptation in human and veterinary neonatology. Viability is granted by some anatomic and physiologic characteristics that allow the normal transition from intrauterine to extrauterine life, in which soon and efficient respiration plays a pivotal starting role. The normal viability of a newborn at birth can be assessed in diverse ways, from the easiest observation of some "vital" behaviors, such as normal soon crying, to the clinical, practical evaluation of some newborn physiologic parameters or reflexes through score systems, such as the Apgar score<sup>18</sup> or the Reflexes score. A first detailed Apgar system score for the newborn dog was proposed in 2009<sup>18</sup>, defining the parameters to be assessed, the timing of assessment, the vitality classes, and the short-term survival prognosis impact. After that, other studies confirmed the usefulness of the Apgar scoring system for the newborn dog viability evaluation at birth, and in most cases also the usefulness as a survival prognostic factor within 24-48 h after birth<sup>3,10,14,21-31</sup>. Likely in human neonatology, in canine newborns also, the Apgar score is important to address the proper assistance to each neonate. According to the newborn's viability class, based on the Apgar score, the first assistance of low-scored newborns includes clearing of the airways, oxygen supplementation, heart stimulation, and, sometimes, drug administration. The Apgar score is also useful to assess the response of the newborn to assistance or resuscitation. During assistance or resuscitation, neonatal support also includes body temperature control and assuring the prompt colostrum assumption.

Congenital anatomical or functional malformations are responsible for a 68% mortality rate in malformed puppies, with about 61% of deaths occurring during the first 2 days of age, and the remaining about 39% between 3 and 30 days of age<sup>32</sup>. The congenital malformation can interfere with the process of neonatal adaptation leading to spontaneous newborn death or may require euthanasia. Unfortunately, only a few malformations can be detected at birth and most remain undiagnosed. Neonatal hypothermia is protective soon after birth when limited in intensity and time, otherwise, it can be responsible for death and increased morbidity. A body temperature of  $33.9 \pm 1.2$  °C has been associated with puppy mortality <7 days of age<sup>22</sup>.

The physiologic neonatal adaptation can also be investigated by analyzing some blood parameters indicating the occurrence of asphyxia, acidosis, and glycemia disturbances.

Asphyxia has been reported to be responsible for 60% of puppies' deaths, 90% of which die within the first 2 d<sup>33</sup>. Asphyxia could lead to a mixed acidosis that normally resolves soon after birth (22). The measurement of blood pH indicates the degree of acidosis and has been reported as a prognostic marker in newborn dogs<sup>34,35</sup>. Acidosis can also be detected by measuring blood lactate concentrations. However, in literature, variable cut-off values have been reported for blood lactate as a predictor of newborn dog mortality<sup>19,36-39</sup>. The available studies are unlikely heterogeneous according to the type of blood analyzed, the site of sampling, the age at sampling, and the type of parturition, all factors that could contribute to the variety of cut-off values.

Hypoglycemia has been reported as a main cause of neonatal mortality in dogs<sup>33,39,40</sup>, and blood glucose measurement as a prognostic factor<sup>41</sup> at birth<sup>10,22,27,40</sup> or 1 day of age<sup>10</sup>.

However, diverse cut-off values of blood glucose at birth, indicating hypoglycemia, to predict mortality have been reported from the above-mentioned studies. On the opposite, also hyperglycemia has been associated with the risk of death in newborn puppies<sup>29,38</sup>.

Due to the canine placenta's characteristics, the newborn dog's immune defence mostly relies on passive immunity achieved through colostrum ingestion. The effectiveness of passive immune transfer depends on colostrum quality, the timing of colostrum intake, and the efficacy of antibody<sup>54</sup>

absorption by the intestinal cells of the newborn. The intestinal absorption rate shows a two-fold decrease from birth to the 4th hour after birth and becomes insignificant at 12-16 hours after birth<sup>42</sup>. The poor immune transfer, detected in 18% of the newborns<sup>43</sup> could be assessed in neonates at 2 days by assessing the IgG serum concentration, since a cut-off value to predict mortality in puppies 2-21 days of age has been identified<sup>43</sup>. At last, even if scarcely investigated in the dog in comparison to other species, also the evaluation of the placenta should be part of the neonatal puppy assessment. Indeed, some studies showed a relationship between morphological and histological aspects of the placenta and the vitality, birthweight, and post-natal growth in puppies<sup>14,44</sup>. The placental efficiency evaluated by its weight was reported to be a useful parameter for identifying puppies at risk of death in the first weeks of age<sup>45</sup>. In conclusion, the prediction of puppy survival at birth must rely on a systematic assessment of all newborns for the relevant clinical parameters, allowing targeted assistance to newborns, to improve neonatal outcomes. Laboratory analysis could be helpful to complete the newborn evaluation or to investigate specific neonatal adaptation disturbances.

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