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Prenatal and Neonatal Adaptations with a Focus on the Respiratory System

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Contents
Among the modifications that occur during the neonatal period, pulmonary development is the most critical. The neonate's lungs must be able to perform adequate gas exchange, which was previously accomplished by the placenta. Neonatal respiratory distress syndrome is defined as insufficient surfactant production or pulmonary structural immaturity and is specifically relevant to preterm newborns. Prenatal maternal betamethasone treatment of bitches at 55 days of gestation leads to structural changes in the neonatal lung parenchyma and consequently an improvement in the preterm neonatal respiratory condition, but not to an increase in pulmonary surfactant production. Parturition represents an important challenge to neonatal adaptation, as the uterine and abdominal contractions during labour provoke intermittent hypoxia. Immediately after birth, puppies present venous mixed acidosis (low blood pH and high dioxide carbon saturation) and low but satisfactory Apgar scores. Thus, the combination of physiological hypoxia during birth and the initial effort of filling the pulmonary alveoli with oxygen results in anaerobiosis. As a neonatal adaptation follow-up, the Apgar analysis indicates a tachypnoea response after 1 h of life, which leads to a shift in the blood acid–base status to metabolic acidosis. One hour is sufficient for canine neonates to achieve an ideal Apgar score; however, a haemogasometric imbalance persists. Dystocia promotes a long-lasting bradycardia effect, slows down Apgar score progression and aggravates metabolic acidosis and stress. The latest data reinforce the need to accurately intervene during canine parturition and offer adequate medical treatment to puppies that underwent a pathological labour.

Introduction

In veterinary medicine, the neonatal period corresponds to the interval between birth and the 14th day of life, that is, the first two weeks of post-natal life. During this stage, important adaptations to countless factors (including thermal, environmental and dietary factors) occur simultaneously with the development of vital functions that were not performed during intrauterine life. For instance, pulmonary respiration develops to guarantee the efficiency of gas exchange, which was previously a placental activity. Therefore, the neonatal period is critical, and it is crucial to study its typical progression to improve the assistance provided to newborns.

Advancements in veterinary neonatology remain scarce because of the particularities of the neonatal period, during which disease progresses quickly with clinical signs that are rarely pathognomonic. No standardized measures available for neonatal assistance have been adopted for different animal species; therefore, veterinary medical actions are rather empirical. For instance, neonatal vitality may be assessed using the Apgar score, which is based on the vital parameters of newborns. Although the Apgar score is widely used in human medicine, no references currently exist to contribute to a standard for dogs. In humans, the gasometric values of umbilical cord blood are routinely assessed to measure the degree of neonatal metabolic and respiratory acidosis and thus establish early corrective measures. However, the blood gasometric values of newborns are not fully known in veterinary medicine.

During normal labour, humans and most domestic animals experience a short period of foetal asphyxia simultaneous with the uterine contractions, which might result in neonatal transient hypercapnia and acidaemia (Ruth and Raivio 1988). In addition to the important role that hypoxia plays at the onset of labour, this stimulus is essential for foetal maturation because it induces the production of pulmonary surfactant, liver and digestive enzymes and epidermal proteins (Martin and Crump 2003). However, when hypoxia lasts too long, it can have serious consequences for newborns, making it an important cause of neonatal mortality and morbidity (Ruth and Raivio 1988).

Respiratory disorders are the most common conditions in human neonatal outpatient clinics and intensive care units, and such disorders are most severe among premature infants. The success of immediate adaptation to extrauterine life depends on appropriate pulmonary function, which includes the morphological, physiological and biochemical maturation of the lung parenchyma. Deficient surfactant production is the main cause of respiratory distress syndrome (RDS) (Miyoshi et al. 1998). In human medicine, the production of pulmonary surfactant by type II pneumocytes may be reliably correlated with the degree of foetal lung maturity and readiness for extrauterine life (Vestweber 1997).

The maturation and growth of the foetal respiratory system are marked by complex and continuous events that begin during intrauterine life and extend into the post-natal period (Bolt et al. 2001). Recent observations suggest that several endocrine factors, including glucocorticoids, play an important role in the regulation of the lung development and in the transition to extrauterine life. In humans, high cortisol levels in the foetal circulation coincide with important events that characterize the structural and functional maturation of the lung, all of which facilitate gas exchange after birth (Bolt et al. 2001). The prenatal use of corticosteroids in humans to induce artificial foetal lung maturation started in 1972 and resulted in a significant decrease in the incidence of RDS among premature newborns (Peltoniemi et al. 2007).

Therefore, the present study sought to compile the latest findings in small animal neonatology, with an emphasis on findings related to the respiratory system's adaptation to the neonatal challenge period.

Propedeutics of the Neonatal Respiratory System

Excluding disorders during labour, the newborns of domestic animal species generally survive the transitional phase without any assistance (Noakes 2001). Nevertheless, alterations in the adaptive functions might occur, especially among weakened newborns and during adverse environmental circumstances. In this regard, appropriate supervision and assistance during the neonatal period are of paramount importance to increasing the odds of survival. In the veterinary neonatal outpatient setting, clinical records tend to be vague or difficult to interpret, it is difficult to collect and interpret laboratory samples, and the clinical progression of diseases occurs very fast. For these reasons, some practical measures aimed at individual and population-based prevention are indispensable for veterinary doctors who wish to make a positive contribution to neonatal medicine.

In humans, the Apgar score is routinely used to assess neonatal vitality at birth. This score analyses the main vital functions of newborns during their first minutes of life and indicates the need to prevent or correct disorders. When analysing the Apgar scores of canines, Lúcio et al. (2009) observed depression of the vital functions immediately after birth in response to the transition between foetal and extrauterine life. However, recovery was appropriate at 5 min of life, and high scores persisted up to 1 h after birth. These findings indicate that some time is needed for newborns to adjust to new functions such as spontaneous respiration, the adaptation of the cardiovascular system to pulmonary gas exchange, the development of metabolic functions that were formerly performed by the placenta, the redirecting of the bloodstream towards vital organs, the acquisition of the muscular tonus needed for feeding and sensitization to external stimuli (Crissiuma et al. 2005).

Isolated assessment of the respiratory rate is not precise enough to assess newborns with possible respiratory disorders because it does not exhibit a significant correlation with the blood carbon dioxide pressure (PCO_2) (Silva et al. 2009). Therefore, it is recommended to combine respiratory rate measurement with careful auscultation of the lungs and specifically focused diagnostic exams, such as blood gas assessment. Upon thorough examination of the respiratory system (pulmonary auscultation), 78% of eutocic canine neonates exhibit irregular respiratory patterns associated with mild-to-moderate breath sounds immediately at birth, which decreases to 28% within the first 5 min after delivery (Silva et al. 2009).

Uterine contractions during labour induce a physiological reduction in the blood flow from the mother to the foetus, with a consequent decrease in the partial pressure of oxygen (PO_2) in the foetal blood. When hypoxia is severe or long lasting, it produces a significant reduction in the PO_2 and reflex cerebral vasodilation combined with peripheral vasoconstriction (Siristatidis et al. 2004). Metabolic component (base excess and bicarbonate [HCO_3^-]) measurement can identify those newborns at greater risk of developing acute or chronic sequelae of intrauterine asphyxia (Andres et al. 1999). According to pH measurements, canine neonates exhibit acidosis at birth that is both metabolic (low base excess and HCO_3^-) and respiratory (high PCO_2), which is called mixed acidosis (Lúcio et al. 2009). At birth, pulmonary expansion begins progressively, which does not allow gas exchange to attain immediate balance and thus favour the development of the mixed acidosis observed at this stage (Crissiuma et al. 2005). One hour after birth, canine puppies still exhibited acidosis because despite a significant increase, the pH values remained below the reference values (Lúcio et al. 2009). The assessment of the base excess and HCO_3^- variables at this point shows that the metabolic component has not reached its balance. Adaptation to pulmonary respiration after birth is an important factor in the recovery of the acid–base balance. An appropriate respiratory rate favours the elimination of CO_2, decreasing its blood concentration. However, a 1-h period after birth was not sufficient for the metabolic imbalance to achieve full recovery, despite considerable improvement (Lúcio et al. 2009). In addition, the PO_2 reduction and the increase in neonatal metabolism favour the development of anaerobiosis, which maintains the state of metabolic acidosis.

Newborns are physiologically adapted to survive under restricted oxygen conditions. In fact, canine newborns exhibit physiological hypoxia immediately after birth (Lúcio et al. 2009). In the subsequent hours, the high requirements of oxygen aim to supply the higher rates of foetal metabolism. However, gas exchange balance is not achieved immediately, and newborns undergo a period of physiological hypoxia that increasingly worsens throughout the first hour of life (Lúcio et al. 2009).

Direct diagnosis of neonatal respiratory distress is not reliable when it is based exclusively on the clinical examination because the signs that newborns exhibit are minimally characteristic and can be related to non-pulmonary causes. Thus, diagnostic exams are needed. Radiographic assessments of newborns' lungs are performed frequently in human medicine to establish the integrity of the lung parenchyma and the alveolar and bronchiolar content of infants who exhibit any type of respiratory disorder. Radiographic examination contributes to the differential diagnosis among several pulmonary pathological disorders and can indicate the required treatment, which depends upon the degree of pulmonary distress, the lung content (e.g. amniotic fluid, meconium, blood) and the patient's clinical symptoms. In dogs with RDS, radiographic images exhibit alveolar, interstitial and peribronchial patterns across the lung lobes (Järvinen et al. 1995). High respiratory rate associated with high mobility of the chest walls makes it difficult to obtain clear radiographic images and can hinder the diagnosis of the radiographic patterns as diffuse, reticular or interstitial (Silva et al. 2009). It is worth noting that chest X-rays of puppies exhibit general interstitial opacity because of the lower volume of air in the alveoli (Haskins 1977). Therefore, Silva et al. (2009) suggest that chest radiographs should be used as an adjuvant diagnostic tool in conjunction with clinical assessment and blood gas measurement in the detection of moderate to severe hypoxaemia and severe pulmonary oedema. Despite such shortcomings, radiographic assessments can contribute to the diagnosis of disorders in the reabsorption of foetal pulmonary fluids and alveolar expansion. In one study, 83% of canine puppies born after eutocic vaginal labour did not exhibit radiographic alterations; however, mild general opacity with a poorly defined cardiac silhouette was observed in 11% of puppies, and moderate pulmonary opacity with a poorly defined cardiac silhouette and bronchia compatible with pulmonary oedema was observed in only 6% of puppies (Silva et al. 2009).

Foetal and Neonatal Pulmonary Development and Maturity

The development of the foetal respiratory system is a complex and continuous process that includes pulmonary growth and maturation. This process begins early in gestation and extends into adulthood, and it can be divided into five developmental phases: embryonic, pseudoglandular, canalicular, saccular and alveolar (Miyoshi et al. 1998). Sipriani et al. (2009) observed the lung development of canine foetuses throughout gestation and found that the pseudoglandular phase occurred between gestational days 35 and 46 and that the onset of the canalicular and saccular phases began on gestational days 48 and 56, respectively, whereas alveolar development began only after birth and extended throughout the neonatal period.

The appropriate performance of the respiratory function at birth depends not only on the proper development of the lung structure but also on multiple factors, including the sufficient synthesis and secretion of surfactant. The physicochemical interactions between the molecules of air and water inside the alveoli result in a variable force known as superficial tension. The magnitude of this force increases at the end of expiration because of the reduction in the alveolar diameter, and it tends to cause alveolar collapse (atelectasis) (Rebello and Diniz 2000).

In human medicine, prematurity is the main cause of neonatal morbidity and mortality. It is associated with 75% of deaths, and it is directly related to respiratory disorders and infectious and neurological complications (Rades et al. 2004). Among the countless complications of prematurity, RDS, which is related to structural immaturity and the inappropriate production of surfactant, is the most severe medical disorder found in human newborns (Hermansen and Lorah 2007).

Betamethasone is used in human perinatology as the first-choice treatment to improve neonatal pulmonary function. The betamethasone preparation currently used to promote improvement of the pulmonary function includes equal parts of betamethasone sodium phosphate, which is soluble and quickly absorbed into the tissues after administration, and betamethasone acetate, which acts as a reservoir from which betamethasone is slowly absorbed (Moss et al. 2003). The pulmonary function improvement that results from prenatal glucocorticoid use is caused by structural and functional changes in the lungs. The binding of glucocorticoids to the lung parenchyma cells (i) stimulates surfactant protein and phospholipid production, (ii) induces cellular maturation and differentiation and changes in the interstitial tissue components and (iii) regulates the metabolism of the pulmonary fluids (Bolt et al. 2001). In dogs, maternal corticotherapy (0.5 mg/kg of betamethasone phosphate and acetate) on gestational day 55 (post-ovulation) improved the clinical evolution of newborns born on gestational day 57. These newborns exhibited positive correlations between their Apgar scores and the formation of septa and subsaccules in the lungs (Regazzi 2011). Therefore, clinical improvement in such cases is related to the more efficient gas exchange that results from the structural alterations induced by prenatal betamethasone administration (Regazzi 2011). In addition, premature puppies' compensatory response to acid–base imbalance is better with maternal betamethasone therapy, during which the pH and PCO_2 normalize at 240 min after birth. This finding indicates that betamethasone treatment improves the pulmonary gas exchange capacity (Regazzi 2011).

The primary effect of prenatal corticotherapy in pulmonary disorders is structural maturation, which improves the pulmonary function after birth (Ballard and Ballard 1995). According to Regazzi (2011), premature puppies subjected to maternal betamethasone therapy had better visualization of the lung parenchyma on chest radiographs; the general opacity was diminished, and the volume of pulmonary air was larger. In addition, the rates of air bronchogram sign and atelectasis are lower as a result of improved air passage and pulmonary expansion.

Respiratory Adaptation According to the Obstetric Condition

The main disorders during the neonatal period are caused by hypoxia secondary to alterations in the uteroplacental circulation and disorders of the umbilical cord during intense and prolonged uterine contractions (Siristatidis et al. 2004). The strength of contractions and the pressure on the pelvic area give rise to an acidotic environment and foetal hypoxia. Prolonged or intermittent asphyxia *in utero* or during labour decreases newborns' vitality and reduces their ability to adapt to extrauterine life (Herpin et al. 1996). In fact, Lúcio et al. (2009) showed that canine newborns born after dystocic labour that required obstetric assistance exhibited higher degrees of depression at birth, which demonstrates that the stress associated with dystocia affects the vitality of newborns. Dystocia affects the neonatal period of adaptation and lengthens the duration of neonatal hypoxia and anaerobiosis.

Silva et al. (2009) found that the respiratory rate at 60 min of life was significantly lower in puppies born by caesarean section (C-section) compared with those born after eutocic vaginal labour. Additionally, 85% of puppies born by C-section exhibited cyanosis of the mucous membranes at birth, whereas only 30% of those born after a normal delivery did. For this reason, newborns surgically delivered exhibited significantly lower Apgar scores during the first minutes of life (Silva et al. 2009).

Pulmonary respiration in newborns is triggered by tactile and thermal stimuli and the moderate deprivation of air caused by the labour mechanism (Vestweber 1997). Upon the first inspiration, only a portion of the alveoli are insufflated; thus, any influence might threaten appropriate alveolar expansion. During this phase, the lungs are also filled with amniotic fluid containing a low concentration of soluble oxygen. During the physiological mechanism of labour, there is a concomitant diminution of the synthesis and a greater absorption of pulmonary fluids, and surfactant secretion is stimulated. Indeed, newborns born by C-section exhibit lower lecithin/sphingomyelin ratio (surfactant phospholipids) values compared with vaginal-delivered newborns (Silva et al. 2009). We believe that when C-sections are performed before the physiological onset of labour, the mechanisms for final pulmonary maturation are not appropriately activated. Madar et al. (1999) demonstrated that pulmonary function alterations were significantly higher in human full-term infants born by elective C-section compared with those born after normal labour. We believe that the lack of stimuli from compression along the vaginal canal in surgically born neonates reduces the reflex respiration. Consequently, the frequency of pulmonary alterations in the chest radiographs is higher (30%), especially in the caudal lung lobes. Therefore, gas exchange is less efficient during the initial inspirations and results in tissue hypoxia (Silva et al. 2009).

Final Considerations

The field of neonatology is relatively new, even in human medicine. Nevertheless, the field has advanced considerably in the past five decades, keeping pace with the progression of research in other fields of medicine. This status in veterinary medicine is undoubtedly due in part to the importance of neonates to their families and appropriate public health control.

Neonatology represents a shift in veterinary medicine, in which individuals are typically seen as patients independent of their age range. For this reason, research in this area might provide the data needed to make medical investment possible and to change the idea that neonatal losses are because of fatalities. With the new knowledge arising from scientific research in neonatology, veterinary doctors will no longer be able to refuse medical assistance to canine newborns and their mothers.

The adoption of a feasible system of veterinary neonatal analysis must first classify puppies into two categories. An Apgar score adapted to veterinary medicine will allow differentiation between healthy and ill newborns. For unhealthy neonates, further analysis will allow clinicians to establish a diagnosis and define corrective measures. It is worth noting that an analysis of the length of evolution and newborns' adaptation to extrauterine life must be prioritized when providing them with assistance. Puppies require medical attention well after delivery to establish whether the adaptive phase will occur without any issue. Blood gasometric assessment will confirm neonatal adjustment to the first hours of life, especially in regard to gas exchange and tissue oxygenation.

Current researchers have produced relevant clinical data for veterinary neonatology. Nevertheless, several scientific questions remain or emerged from these studies. Future research in this area must prioritize the discovery of new physiological data corresponding to the neonatal period and must contribute to the establishment of practice patterns specific to pregnant and parturient females and newborns.

Conflicts of interest

None of the authors have any conflicts of interest to declare.

Author contributions

All authors carried out the experiments. CIV drafted the paper.

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