https://doi.org/10.17221/86/2018-VETMED

Therapeutics of neonatal asphyxia in production animals: a review

*Jose Sanchez-Salcedo[1], Herlinda Bonilla-Jaime[2], Miguel Gonzalez-Lozano[3], Socorro Hernandez-Arteaga[5], Victoria Greenwell-Beare[4], Xochil Vega-Manriquez[5], Milagros Gonzalez-Hernandez[5], Hector Orozco-Gregorio[5]**

[1]*Doctoral Program in Biological Sciences and Health, Universidad Autónoma Metropolitana, Iztapalapa, Mexico City, Mexico*
[2]*Department of Reproductive Biology, Universidad Autónoma Metropolitana, Iztapalapa, Mexico City, Mexico*
[3]*Department of Animal Production: Swine and CEIEPP, Universidad Nacional Autónoma de México (UNAM), Mexico*
[4]*School of Veterinary Medicine and Zootechnics, Universidad del Valle de México, Coyoacán, Mexico City, Mexico*
[5]*Faculty of Agronomy and Veterinary, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico*

**Corresponding author: hector.orozco@uaslp.mx*

Citation: Sanchez-Salcedo J, Bonilla-Jaime H, Gonzalez-Lozano M, Hernandez-Arteaga S, Greenwell-Beare V, Vega-Manriquez X, Gonzalez-Hernandez M, Orozco-Gregorio H (2019): Therapeutics of neonatal asphyxia in production animals: a review. Veterinarni Medicina 64, 191–203.

Abstract: The aim of this review is to assess the different treatments and therapeutic protocols used for neonatal asphyxia in animal production. Perinatal asphyxia is considered to be one of the main non-infectious causes of neonatal mortality in the majority of domestic mammals. However, its incidence in intensive animal production is increasing because of a series of implemented strategies aimed at improving and increasing production. For example, through the application of genetics, an increase in size and weight in newly born animals has been achieved. Nevertheless, this has resulted in a larger incidence of dystocia associated with oxygen restriction to the-foetus, which elicits metabolic and respiratory acidosis. Furthermore, aside from immediate financial implications when it comes to production, it also has an impact on the welfare of mother and offspring. Regarding the field of animal perinatology, several therapeutic strategies using respiratory and hormonal stimulants, as well as energetic supplements have been evaluated with the aim of preventing perinatal asphyxia and treating neonates with the condition, and also to diminish the incidence of stillbirths associated with it. However, during the last decades this condition has persisted mainly in porcine, equine, ovine and bovine production; for this reason, it continues to be studied extensively.

Keywords: animal perinatology; neonatal mortality; piglets; foals; calves

José Sánchez-Salcedo is enrolled in the Doctoral Program in Biological and Health Sciences at the Universidad Autónoma Metropolitana, and was supported by scholarship No. 337256 from CONACYT, México. Héctor Orozco-Gregorio, Herlinda Bonilla-Jaime and Milagros González-Hernández, were supported as members by the Sistema Nacional de Investigadores (SNI) in Mexico.

https://doi.org/10.17221/86/2018-VETMED

Contents

1. Introduction

During the second stage of labour, foetuses go through intermittent periods of mechanical pressure provoked by uterine contractions that are part of the labour process, which lead to a temporary deprivation of oxygen for the new-born (Yli and Kjellmer 2016). However, in some cases, the intrauterine pressure exercised on the foetus can increase in length and intensity until it becomes pathological. The cumulative effects of uterine contractions during pathologically prolonged labour will lead to cord damage or cord rupture as well as a premature detachment of the placenta which invariably leads to foetal hypoxia. If hypoxia persists due to dystocia, it can have serious negative long-term effects on the survival of the new-born or be immediately fatal (Martz et al. 2017). In many cases, this event has been related to the implementation of both genetic and handling strategies that have been carried out in order to increase and improve animal production – increasing the size of litters and the weight of the product/products can be given as examples (Quiniou et al. 2002; Fix et al. 2010; Vanderhaeghe et al. 2013).

What is more, the inadequate use of labour inducers or accelerants has resulted in alterations in uterine behaviour increasing the number of both stillbirths and new-borns showing evidence of having gone through severe oxygen restriction during labour (Mota-Rojas et al. 2005). However, irrespective of its aetiology one major cause of neonatal death in farm animals is intra-uterine hypoxia during labour. Therefore, from financial and welfare perspectives, there is a high motivation to reduce death rates (Martz et al. 2017). The objective of the present paper is to discuss the different treatments and the different therapeutic protocols used in the prevention and treatment of neonatal asphyxia in the main species of domestic animals used in animal production.

2. Perinatal asphyxia

In human medicine, asphyxia represents one of the main causes of death in the neonatal period; The World Health Organization has calculated that more than a million new-born babies survive asphyxia and all of these present with sequelae such as infantile cerebral palsy, learning disabilities and physical and development problems (WHO 2017). In human medicine, three causes account for three quarters of neonatal mortality cases worldwide: premature births for 29%, asphyxia for 23% and severe infections such as sepsis and pneumonia for 25% of all cases.

On the other hand, in animal production, perinatal asphyxia (PA), regardless of its aetiology, is the main cause of new-born mortality of non-infectious origin. It accounts for 10% to 20% of mortality during the first days of piglet lactation (Alonso-Spilsbury et al. 2005; Baxter et al. 2011; Muns et al. 2016), for 19.5% in foals (Pirrone et al. 2013; Carluccio et al. 2017), 17–30% in puppies (Veronesi et al. 2009; Tonnessen et al. 2012; De Cramer et al. 2017), 2.5–8.6% in calves (Bleul and Kahn 2008; Probo et al. 2012) and 20% in lambs (Robertson et al. 2018). When it comes to porcine production, the costs associated with piglets up until weaning, from gestation to labour, are close to 45.72 dollars (Seddon et al. 2013); therefore, pre-weaning mortality results in significant economic losses for this industry. In the same way, a dead calf during the stage prior to weaning translates into an approximate cost of 57.20 dollars (Retes-Lopez et al. 2013),

https://doi.org/10.17221/86/2018-VETMED

while that of a dead lamb in the perinatal stage is estimated at 100 dollars (Robertson et al. 2018).

Generally, as foetuses advance through the birth canal at the time of birth, they go through intermittent periods of mechanical pressure caused by uterine contractions during labour that lead to temporary oxygen deprivation for the new-born (Yli and Kjellmer 2016). Different studies have characterised uterine contractions during labour in species such as the sow. With regard to this, Olmos-Hernandez et al. (2008) reported that the intensity of uterine contractions in the sow during eutocic labour vary depending on the number of previous births. That is, sows giving birth for the first, third and sixth time presented intensities of 12.30 ± 2.18, 9.30 ± 2.45 and 10.25 ± 1.77 mmHg, respectively, with primiparous mothers showing higher intensity contractions while those giving birth for the fourth time exhibited lower intensity contractions (8.59 ± 2.01 mmHg). These data suggest that in the case of sows, the intensity of uterine contractions is dependent on the number of previous births. In bovines, the intensity of uterine contractions is higher than in sows and it is independent of the number of eutocic labours the female has had, oscillating between 19.6 up to 40 mmHg and lasting for up to 48 hours after labour has finished (Bajcsy et al. 2005).

However, both genetic and handling strategies have been implemented to increase and improve animal production: augmenting the size of the litter and the weight of the product/products represents one such strategy. This has provoked prolonged labour in which the cumulative effects of uterine contractions lead to protracted expulsion and invariably to foetal hypoxia (Martz et al. 2017). On the other hand, the inadequate use of labour inducers or accelerants elicits alterations in uterine behaviour. As an example, it has been shown that the administration of exogenous hormones such as oxytocin during labour in sows can increase uterine activity up to levels that are dangerous for piglets. Uterine over-stimulation provoked by oxytocin diminished blood flow to the uterus and resulted in a state of foetal distress (Gonzalez-Lozano et al. 2009a). In contrast, Gonzalez-Lozano et al. (2012) reported that the administration of vetrabutine hydrochloride, a spasmolytic muscular tropic drug, significantly reduced the incidence of stillborn piglets in sows with dystocia, while the number of piglets born alive without evidence of acute foetal suffering was higher in sows treated with vetrabutine hydrochloride in comparison to the control group.

Regardless of the cause, modified uterine activity during labour results in alterations to neonatal pulmonary ventilation, which in turn, provoke a decrease in the saturation of circulating oxygen and a decrease in oxygen flowing to the brain (Herrera-Marschitz et al. 2014). A reduction in the availability of oxygen is categorised in the following way: Type 1) Hypoxaemia, which involves a reduction in oxygen in arterial blood without necessarily affecting organ and cell functions. Type 2) Hypoxia, which stems from a reduction in oxygen and subsequently in anaerobic metabolism mainly in peripheral tissue and Type 3) Asphyxia, in which hypoxia is extended to central organs and may likely lead to metabolic acidosis (Yli and Kjellmer 2016). When this last type occurs during labour, it is defined as perinatal asphyxia (PA). PA occurs when the gas exchange between mother and foetus is altered and is characterised by hypoxaemia, hypercapnia and ischaemia, which provoke an immediate redistribution of blood flow to vital organs and, therefore, flow to other tissues becomes compromised (Nemeth et al. 2016; Barkhuizen et al. 2017). The indicators for the diagnosis of perinatal asphyxia in human babies and in different domestic species are defined in Table 1. Notice the recent adaptations made to the Apgar scale for its use in domestic animals and the use of equipment to assess acidosis in domestic animals.

In the majority of cases, new-borns with PA will manifest metabolic and respiratory acidosis processes (Orozco-Gregorio et al. 2010, Orozco-Gregorio et al. 2011) that exert a direct impact on well-being and with immediate financial implications for production, even in animals that manage to survive the process. Previous research has shown that those piglets which survived a PA event showed reduced consumption of milk, which is related to an increase in the time required to start suckling for the first time. As a consequence, these piglets had gained less weight by five days after birth (Trujillo-Ortega et al. 2007; Orozco-Gregorio et al. 2008). This has also been reported in calves in which, furthermore, the immunological system was compromised due to failure in the passive transference of immunity stemming from the low consumption of colostrum after the asphyxia episode (Murray and Leslie 2013).

https://doi.org/10.17221/86/2018-VETMED

Table 1. Diagnosis of asphyxia in new-borns of different species

	Species				
	human baby	foal	calf	piglet	lamb
Acidosis indicator	pH < 7.00 EB < 10 mmol/l	Lac > 5.48 mmol/l Cor > 288.55 nmol/l Glu < 5.49 mmol/l	Lac > 6.62 mmol/l pH < 7.21	pH < 7.2 Lac > 5.55 mmol/l pO_2 < 20 mmHg Ca > 1.8 mmol/l meconium staining	pH < 7.1 pO_2 < 10 mmHg
Neonatal vitality scale used	Apgar score 0.3 after 5 minutes	Apgar score modified, viability less than 6	physiological parameters and poor suction response	neonatal vitality scale less than 6 (modified Apgar)	vitality decrease adapted to the Apgar score lesser than 6
Effects and consequences	neurological alterations and/or multi-systemic organic failure	cardiovascular, pulmonary, metabolic and thermoregulatory abnormalities stand out. Equine neonatal sepsis.	reduced vitality, inability to stand up, lack of strength in suction reflex, immunoglobulin absorption and weight gain affected	increase in delay to establish contact with teat, hypothermia	diminished vitality and increase in delay to suck colostrum
Reference	IMSS-632-13 (n.d.)	Knottenbelt et al. (2004); Smith (2002); Nogueira and Lins (2010); Cruz et al. (2017)	Murray et al. (2015)	Mota-Rojas et al. (2006); Gonzalez-Lozano et al. (2009b); Gonzalez-Lozano et al. (2012)	Dutra and Banchero (2011)

Ca = calcium; Cor = cortisol; EB = excess base; Glu = glucose; Lac = lactate; pO_2 = partial pressure of oxygen

As well as the important economic losses caused by PA, the ever-growing awareness of animal welfare (Yeates and Main 2008; Ohl and van der Staay 2012) has resulted in increased interest in studying this phenomenon. This increased focus has the goal of enabling more definitive diagnoses in order to avoid the suffering of the mother and its young as well as to generate and promote new and more effective prevention, intervention and recovery protocols (Bleul and Kahn 2008). In human medicine, the World Health Organization stresses the importance of timing, stating that if available interventions were to reach those who need them at the right time, two thirds or more of the above-mentioned deaths could be prevented.

3. Therapies for oxygen re-establishment in new-borns with asphyxia

3.1 Neonatal re-oxygenation post asphyxia

As pointed out above, not all mammalian foetuses experience hypoxia phases of varying severity during the birth process. However, foetal oxygen restriction can result in intrauterine respiratory stimulation which, if not dealt with through the initiation of spontaneous breathing at the moment of birth, will lead to processes of neonatal apnoea. That is why, in animals such as foals and dogs, artificial ventilation is the standard treatment for apnoea caused by asphyxia. However, because of the equipment and the number of operators needed for ventilation, these procedures cannot be carried out routinely when dealing with farm animals (Bleul et al. 2010). Furthermore, the indiscriminate or inadequate use of this type of intervention may potentially be toxic for various organs through the production of reactive oxygen species (ROS) (Figueira et al. 2016), as ROS production induces oxidative stress, which in turn affects several aspects of organismal physiological with different pathological consequences (Perrone et al. 2017).

Clinically, oxidative stress is inherent to re-oxygenation, and is a reason why the subsequent production of free radicals worsens brain lesions (Herrera-Marschitz et al. 2014). At an experimental level, it was proven that exposure to 100% oxygen for 30 minutes in new-born sheep results in a significant increase in lipid peroxidation, a key

https://doi.org/10.17221/86/2018-VETMED

indicator of oxidative stress (Perrone et al. 2017). In another study, also carried out in new-born sheep, prolonged ventilation with 100% oxygen for 30 minutes caused an increase in oxygen brain tissue pressure in comparison to those sheep undergoing 3-min oxygenation (0.1 kPa–56 kPa vs 0.1 kPa–4.2 kPa, respectively). This increase in oxygen tissue pressure has only been reported under hyperbaric conditions, which suggests the need to limit oxygen exposure for asphyxiated new-borns (Perez-de-Sa et al. 2009).

In contrast, research in other species in which lower oxygen percentages were used, gave satisfactory results. For example, Herpin et al. (2001) showed that new-born piglets with PA who were administered inhaled oxygen at 40%, showed lower blood lactate concentrations in comparison to the control group (3.79 vs 6.46 mmol/l, respectively). As a consequence, blood pH values were different between the two groups (7.40 vs 7.35, respectively). The authors suggested that the results were due to an immediate supply of oxygen that stimulated oxidative metabolism and the aerobic oxidation of glucose, supplying the piglet with additional ATP (adenosine triphosphate). It is important to point out that lactate and pH are two of the main indicators of PA (Orozco-Gregorio et al. 2008; Orozco-Gregorio et al. 2011). In contrast, Zaleski and Hacker (1993) did not find differences either in the number of stillborn piglets or in new-borns with low life expectancy born to mothers to whom supplementary oxygen was provided during labour.

Also, it has been shown that the use of an air chamber during the handling protocol of the new-born can be a good option for recovery. This is due to the fact that it reduces the damage caused by free radicals that are secondary to direct oxygenation, diminishing the possibility of oxidative stress and multi-organ damage (Baxter et al. 2011). In this way, research carried out in new-born pigs with hypoxaemia and induced meconium aspiration showed that these can be reanimated in air chambers or with 100% oxygen for 120 minutes with satisfactory results in both procedures (Tollofsrud et al. 2002). However, administering oxygen at 80 or 100% for periods of eight or more hours causes irritation to the breathing passages resulting in retrosternal discomfort, nasal congestion, pharynx inflammation and cough. The results obtained suggest that O_2 toxicity is due to the production of the superoxide anion, a free radical produced by an excess of oxygen. This excess oxygen favours the transfer of xanthine dehydrogenase to xanthine oxidase using oxygen as substrate, which generates high amounts of superoxide anion, thus provoking oxidative stress (Vento et al. 2005). In the same way, the release of excitotoxic amino acids, cellular proteolysis, nitric oxide synthesis and the circulation of inflammatory substances such as cytokines, have been implicated in brain damage during PA (Xu et al. 2015) where ischaemic-hypoxic encephalopathy is one of the most severe consequences (Nemeth et al. 2016). Ischaemic-hypoxic encephalopathy is therefore the result of a combination of brain oxygen reduction (hypoxaemia) and/or the reduction in perfusion (ischaemia).

3.2 Methylxanthines

Methylxanthines are a group of bronchodilator drugs also known for mediating anti-inflammatory and neuroprotector effects in chronic degenerative illnesses (Lee et al. 2016; Endesfelder et al. 2017). Moreover, they have been used as respiratory stimulants in the treatment of apnoea and hypoxia in premature humans (Skouroliakou et al. 2010; Park et al. 2015), as well as in the physiometabolic recovery of foals (Wilkins 2003; Katz 2006), calves (Bleul et al. 2010) and pigs (Orozco-Gregorio et al. 2010; Orozco-Gregorio et al. 2011) with neonatal asphyxia. Four different mechanisms of action have been described for methylxanthines: (1) The mobilisation of intracellular calcium, (2) The inhibition of phosphodiesterase, (3) The modulation of GABA receptors and (4) The antagonism of adenosine receptors. The blocking of adenosine receptors, however, seems to be mainly responsible for many of the effects of methylxanthines on the central nervous system (Onatibia-Astibia et al. 2016).

In new-born foals with PA, episodes of hypoxaemia and hypercapnia are common. With respect to this, Wilkins (2003) has suggested that in those foals with abnormal breathing patterns and with periods of post-labour apnoea, the administration of caffeine either through the rectum or orally (10 mg/kg) can function as an adjuvant therapy in respiratory support. However, foals with respiratory acidosis that develops as a compensatory mechanism against metabolic alkalosis will not respond to treatment with this methylxanthine. Lu et al. (2006) suggest that in foals with respiratory depression or

https://doi.org/10.17221/86/2018-VETMED

hypercapnia, the administration of caffeine could improve breathing without the need to implement therapeutic protocols with mechanical ventilation.

In the case of porcine production, it has been shown that the oral administration of caffeine (20 mg and 35 mg) in new-born piglets with PA reverses the alterations in the acid-base balance related to the restriction of oxygen suffered by the animal 24 hours after its administration. This is achieved through an increase of blood triglyceride and glucose concentrations (Orozco-Gregorio et al. 2010). In another study, the administration of 35 mg subcutaneously to new-born piglets with PA resulted in an increase in glucose concentrations and a decrease in pCO_2 levels as well as weight gain that was 19% greater in comparison to the control individuals. Nevertheless, these results were observed only in new-borns whose weights exceeded 1100 g (Orozco-Gregorio et al. 2012).

The results obtained in the research mentioned above have been questioned from a practical point of view as it has been pointed out that both ways of caffeine administration (oral and subcutaneous) are difficult to carry out on porcine farms. Thus, Superchi et al. (2013) have proposed that prophylactic caffeine administration in food to pregnant sows before labour starts improves thermoregulation capacity in the newly born in comparison to the control group (39.31 ± 0.10 °C vs 38.83 ± 0.08 °C), which increases their viability. Equally, the piglets of treated sows exhibited lower concentrations of biopterin, a co-factor in the synthase of nitric oxide and which was used in this experiment as an indicator of the neuroprotective effect of caffeine in the face of adverse reactions akin to PA. More recent studies have determined the effects of 27 mg/kg caffeine intake orally in sows 24 hours before labour. In this study, caffeine did not affect the weight of piglets born to the treated mother; however, they did show a better capacity to adapt to life outside the uterus (Superchi et al. 2016). The effect of caffeine has also been assessed in species such as sheep. Recently, Robertson et al. (2018) observed that the administration of 20 mg/kg caffeine to pregnant sheep reduced lamb mortality from 30% to 9% in the first week of lambing.

Theophylline is another methylxanthine that has been assessed in the recovery of new-borns with asphyxia. In new-born bovines, Bleul et al. (2010) compared the effects of administering theophylline versus doxapram. Their results showed that doxapram – but not theophylline – led to an immediate increase in respiratory rate. Arterial pCO_2 decreased 30 seconds after doxapram administration, but decreased within 120 min after theophylline administration. Pulmonary vascular resistance also increased after doxapram administration and decreased after theophylline administration. The authors concluded that doxapram had a more pronounced and much faster effect on respiratory rate and on the elimination of CO_2 compared to theophylline. However, the administration of doxapram does carry the potential for cardiovascular side effects. Therefore, caffeine has been shown to be more effective for PA in comparison to the other methylxanthine due to the possibility daily dosing at the beginning of its therapeutic action and because of its minimum adverse effects (Park et al. 2015; Onatibia-Astibia et al. 2016). Also, the therapeutic doses of caffeine are much lower than the toxic levels (5 to 25 μg/ml and 40 μg/ml, respectively) in comparison to those of theophylline (7 to 12 μg/ml and 20 μg/ml, respectively). Its half-life in neonates is up to 103 hours versus 20 hours in theophylline, which allows for longer bio-availability in the organism (Natarajan et al. 2007).

In this way, caffeine acts to reduce the frequency of apnoea and hypoxia through the non-selective antagonism of adenosine receptors, improves respiratory functions through its bronchodilator effect, reduces diaphragmatic fatigue, and increases muscular resistance and the secretion of catecholamines (Park et al. 2015; Yadegari et al. 2016). Similarly, as it is highly liposoluble and has a low molecular weight, caffeine passes through the placental barrier easily (Yadegari et al. 2016) and can thus be used in a prophylactic way during gestation. Therefore, therapy with methylxanthines such as caffeine is highly attractive mainly in new-born farm animals with PA due to the ease of administration and to the minimal adverse effects, which means it can improve survival rates as well as neurodevelopment in new-borns.

4. Energy-focused therapies in the treatment of new-borns with asphyxia

During PA, an immediate complication stemming from the absence of oxygen is the development of encephalopathy. This is the result of the combination of a reduction in brain oxygen (hypoxaemia)

https://doi.org/10.17221/86/2018-VETMED

and/or a reduction of perfusion (ischaemia) and oxygenation to the brain. During the acute stage of brain damage, neuronal cell death occurs through necrosis, as a result of brain energy depletion, and even though metabolic energy levels recover in the brain after a few hours a cascade of biochemical events is activated, resulting in neuronal apoptosis and consequently severe brain damage (Filippi et al. 2012). This is why early energy supply failure is considered a very important factor in the survival of the new-born. One of the alternatives for therapeutic intervention is the administration of molecules that can affect energy production through enzymatic ways with the aim of reducing the extent of damage (Valenzuela-Peraza et al. 2014; Declerck et al. 2016; Ellery et al. 2016).

4.1 Thiamine pyrophosphate

During the acute phases of hypoxic ischemic encephalopathy (HIE), neuronal cell death occurs by necrosis occurs as a result of a depletion of brain energy. Even at a few hours post-asphyxia, after commencement of aerobic energy metabolism and replenishment of glucose levels, the previously initiated apoptosis produces severe lesions in the brain (Orozco-Gregorio et al. 2008). In regards to this, one of the therapeutic agents studied for its possible neuroprotective effect is thiamine, a vitamin that carries out its metabolic function mainly through thiamine pyrophosphate (TPP), which is an indispensable co-factor in the activation of dehydrogenase pyruvate, alpha-ceto dehydrogenase glutarate, the alpha-ceto dehydrogenase acid and the transketolase enzymes involved in energy generation through the Krebs cycle (Sicilia-Argumedo et al. 2007; Valenzuela-Peraza et al. 2014).

Research carried out by Valenzuela-Peraza et al. (2014) in neonatal rats with experimentally induced hypoxia, showed that, histologically, the animals given TPP an hour before suffering hypoxia exhibited less brain damage in the motor cortex, somatosensory cortex and in the striate cortex in comparison to the control group. In the same research, the animals given TPP after hypoxia showed no significant changes in the same brain areas. These results suggest that once the process of cellular demise has started, it is practically impossible to revert it, even though other physiometabolic parameters such as pH, $PaCO_2$ and PaO_2 could be stabilised regardless of when exactly TPP is administered.

Additionally, more recent research carried out in rabbit foetuses by Jimehynez-Bravo et al. (2016) showed that TPP is capable of modifying some biochemical parameters during ischaemia *in utero* and during ensuing reperfusion. As one example, the levels of foetal glucose were lower in foetuses without treatment in comparison to those foetuses that received TPP possibly with the aim of preserving energy metabolism under hypoxic conditions.

Therefore, the neuroprotective effects of TPP can be explained through 1) The strengthening of the antioxidant system due to the capacity of TPP to capture free radicals, 2) The reduction in the excessive accumulation of excitotoxins involved in cell death such as glutamate and 3) The intracellular reduction in calcium accumulation (Valenzuela-Peraza et al. 2014). TPP research in animals has been geared towards clinical use in humans; however, in the future, it will be important to carry out research that explicitly focuses on direct use in veterinary medicine.

4.2 Creatine

Experimental studies with animals have shown that amino acids such as creatine, which are endogenously produced from glycerine, methionine and arginine in the liver, kidneys and pancreas, provide neuroprotective effects against ischaemic and oxidative alterations (Sullivan et al. 2000). The main metabolic role of creatine is to combine with a phosphate group and form phosphocreatine through creatine kinase enzymatic reactions. In this way, while ATP is degraded into ADP (adenosine diphosphate) and phosphate thus providing energy for metabolic activity, the energy released from the hydrolysis of PCr (phosphorylcreatine) can be used as a buffer to re-synthesise ATP. This helps to maintain the availability of ATP particularly under anaerobic conditions and those of extreme physical effort (Kreider et al. 2017).

Creatine has been shown to directly improve mitochondrial energy metabolism as well as to act as a weak antioxidant through the ADP re-phosphorylation via phosphocreatine. These properties mean that the reaction between creatine and phosphocreatine can prevent cytosolic acidification, particularly under hypoxic conditions, by pro-

https://doi.org/10.17221/86/2018-VETMED

tecting cells from the damage associated with an acute hypoxic event (Ellery et al. 2016). In regards to this, Ireland et al. (2008), using an experimental model of intra-partum hypoxia in the spiny mouse, showed that creatine added to the feed of gestating mothers (5% of creatine monohydrate in isocaloric pellets) increased neonatal survival up to 95% and also improved the growth rate of the offspring up to the 15th day after labour. Moreover, it has been shown that structural and functional hypoxic damage to the new-born's diaphragm can be reduced by maternal supplementation with creatine probably because this amino acid provides energy for muscular contraction and allows maintenance of ATP synthesis during physical activity (de Camargo Ferraz et al. 2006; Dickinson et al. 2014).

In spiny mice whose diets were enriched with 5% creatine during gestation, exhibited a transfer of this amino acid to the foetus; levels of creatine were increased by 10% to 30% in foetal tissues such as the heart, liver, kidney and muscles without any evidence of harmful effects on the mother and the new-born after PA (Dickinson et al. 2014).

Similarly, as with the TPP described above, there has been no research carried out on animals from other species. It would be important to develop PA treatment protocols on domestic animals.

4.3 Fatty acids

When it comes to supplementing individuals with asphyxia with fatty acids, collagen peptides derived from salmon skin through hydrolysis have shown to be effective in improving physiological and neuro-behavioural development in rats that experienced PA. This manifested as better performance in learning and memory tasks that are part of the Morris water navigation task and was possibly connected with a reduced level of oxidative damage to the brain. Additionally, supplemented rats gained significantly more weight in comparison to those subjected to asphyxia without treatment (Xu et al. 2015).

However, in production animals no significant differences were found in the time required to initiate first suckling amongst piglets born to sows whose diets were augmented with tuna poly-unsaturated fatty acids from day 92 of gestation, compared to piglets born to sows without treatment and to those born to sows treated with fatty acids from the start to day 91 of gestation (Rooke et al. 2001). It is worth pointing out that the time required for neonates to begin suckling at the mammary gland has been one of the most important indicators to determine vitality and viability in new-born piglets (Herpin et al. 1996; Trujillo-Ortega et al. 2007; Orozco-Gregorio et al. 2008).

Cordoba et al. (2000) also reported a decrease in piglet mortality before weaning upon addition of salmon oil to the diet of gestating sows. Meanwhile, Declerck et al. (2016) reported that supplementation of underweight piglets (< 1 kg) with medium- and long-chain fatty acids (Vigorol®) did not have any effect on the improvement of weight upon weaning (5.15 ± 0.091 kg vs 5.69 ± 0.092 kg) nor on the colostrum consumption in comparison to the control group. The authors ascribed this to the possibility that supplementing *per se* reduces appetite, meaning that the treated new-borns are less likely to look for the mother's teat. In accordance with such results, research carried out by Petzold et al. (2014) found that the addition of linoleic acid to bovine diets 21 days before labour does not modify the weight of the offspring.

In other research carried out with the aim of improving performance and vitality in calves straight after labour, Moallem and Zachut (2012) assessed supplementation with three fatty acids crucial for the development of bovine foetuses to the diets of gestating bovines and its concentrations in the plasma of new-borns: linoleic acid, docosahexaenoic acid and eicosapentaenoic acid. No differences were observed in linoleic acid and eicosapentaenoic acid concentrations in calf blood plasma. However, docosahexaenoic acid was 1.9 times larger in comparison to the control calves. According to the authors, this is probably due to the fact that docosahexaenoic acid is essential in foetal development.

In general, supplementing with energy-producing compounds in order to improve viability and vitality in new-borns is broadly applied. Nevertheless, scientific evidence regarding its efficiency is scarce (Declerck et al. 2016) and particularly, the effect observed will depend on the type of fatty acid used (Moallem and Zachut 2012).

5. Melatonin

During gestation, even in normal periods, oxygen demands go up and results in an increased

https://doi.org/10.17221/86/2018-VETMED

rate of reactive oxygen species production (ROS). However, the low antioxidant capacity of new-borns contributes to the pathogenesis of several prenatal conditions associated with exposure to free radicals (Marseglia et al. 2016). For this reason, melatonin seems to be an ideal alternative for these prenatal conditions because of its capacity to capture ROS, as well as its function in blocking the excitotoxic cascade and in modulating neuro-inflammatory passageways, mechanisms known to be involved in the pathogenesis of prenatal brain damage (Colella et al. 2016; Arteaga et al. 2017).

Experimental research carried out by Miller et al. (2005) in sheep foetuses exposed to an acute *in utero* bout of asphyxia, showed that the administration of melatonin as a prophylactic measure in gestation between 1 to 4 and 1 to 7 days resulted in a significant decrease of the free radical OH (hydroxyl free radical). In other research, Welin et al. (2007) showed that the administration of melatonin (20 mg/kg, *i.v.*) reduces cell death in the brain of the ovine foetus after PA, which was induced through the occlusion of the umbilical cord. In this study, the administration of melatonin to the foetus resulted in a decrease in microglia activity and in the concentration of 8-isoprostane after the occlusion of the umbilical cord in ovine foetuses. The 8-isoprostane molecule was considered to be an inflammatory marker of oxidative stress. However, melatonin did not have effects on metabolic acidosis and on blood gases associated with the oxygen restriction.

Finally, in other research carried out in piglets, the administration of intravenous melatonin (5 mg/kg/h) 10 minutes after an experimental hypoxic event resulted in increased neuroprotection through an increase in the brain's energy metabolism as assessed by magnetic resonance spectroscopy (Robertson et al. 2013). In regards to this, Arteaga et al. (2017) proposed that the repeated dosing of melatonin for up to 24 to 48 hours after a hypoxic-ischaemic event is more effective, suggesting a dose-dependent effect in neuroprotection. However, melatonin usage in production animals is not viable on the whole due to the fact that its application is still in the experimental phase. Meanwhile, in human new-borns with PA its application is geared toward avoid the secondary effects of asphyxia during the reperfusion period with the aim of improving neurodevelopment in individuals who suffered asphyxia during labour.

6. Implications

In polytocous species such as pigs, high productivity is defined as a large number of new-born piglets, which has increased the incidence of weakness and of stillbirths (Gonzalez-Bulnes et al. 2016). On the other hand, monotocous species such as sheep, goats, cows and horses have fewer offspring, which has allowed a larger investment in maternal care required by the offspring, maximizing survival rates (Mellor and Stratford 2004).

Several factors have considerably increased the levels of production in species destined for human consumption, which has secondary implications (Gonzalez-Bulnes et al. 2016). In regard to this, nowadays PA is a recurring phenomenon in animal production; new-borns who do not die at a primary or secondary stage as a result of hypoxia during labour, are often nevertheless no longer compatible with post-natal life, and are neither capable of thermoregulation nor of seeking the maternal teat in order to initiate suckling conduct (Dwyer 2008). Also, the new-borns that survive asphyxia episodes turn out to be the weakest in the litter and consume less food, which subsequently hampers weight gain resulting in difficulties in reaching the target weight (Gonzalez-Bulnes et al. 2016).

Therefore, neonatal mortality in animal production can be considered as an indicator of poor welfare; that is, a production system with high levels of post-partum losses is evidently not providing for adequate animal welfare (Dwyer 2008). Consequently, there is an imperative need to investigate prevention and therapeutic strategies suitable to tackle PA.

7. Conclusions

Asphyxia during the prenatal period in domestic animals has emerged as the main non-infectious cause of neonatal death. Particularly in animal production, the sequelae of a decrease in foetal and new-born oxygenation complicate the process of normal labour, which decreases the reproductive efficiency of the females. It also compromises the final commercial quality of the surviving offspring in species such as cows and pigs and increases production costs in larger species such as horses and cows as more complicated obstetric and surgical manipulations are required. Moreover, several

https://doi.org/10.17221/86/2018-VETMED

therapeutic interventions such as immediate re-oxygenation involve complex methodologies with an ensuing increase in production costs, which in practice is not viable. The administration of several drugs that aim to improve physio-metabolic variables in new-borns with asphyxia is the first line of therapy for this condition. Nevertheless, there is currently no clear evidence of the effectiveness of some of the proposed treatments; for this reason, the correct pharmacological intervention in each case must take into account the type of asphyxia and the animal species in question.

8. References

Alonso-Spilsbury M, Mota-Rojas D, Villanueva-Garcia D, Martinez-Burnes J, Orozco H, Ramirez-Necoechea R, Mayagoitia AL, Trujillo ME (2005): Perinatal asphyxia pathophysiology in pig and human: a review. Animal Reproduction Science 90, 1–30.

Arteaga O, Alvarez A, Revuelta M, Santaolalla F, Urtasun A, Hilario E (2017): Role of antioxidants in neonatal hypoxic-ischemic brain injury: New therapeutic approaches. International Journal of Molecular Sciences, doi: 10.3390/ijms18020265.

Bajcsy AC, Szenci O, Doornenbal A, van der Weijden GC, Csorba C, Kocsis L, Szucs I, Ostgard S, Taverne MA (2005): Characteristics of bovine early puerperal uterine contractility recorded under farm conditions. Theriogenology 64, 99–111.

Barkhuizen M, van den Hove DL, Vles JS, Steinbusch HW, Kramer BW, Gavilanes AW (2017): 25 years of research on global asphyxia in the immature rat brain. Neuroscience & Biobehavioral Reviews 75, 166–182.

Baxter EM, Jarvis S, Sherwood L, Farish M, Roehe R, Lawrence AB, Edwards SA (2011): Genetic and environmental effects on piglet survival and maternal behavior of the farrowing sow. Applied Animal Behaviour Science 130, 28–41.

Bleul U, Bircher B, Jud RS, Kutter APN (2010): Respiratory and cardiovascular effects of doxapram and theophylline for the treatment of asphyxia in neonatal calves. Theriogenology 73, 612–619.

Bleul U, Kahn W (2008): Monitoring the bovine fetus during stage II of parturition using pulse oximetry. Theriogenology 69, 302–311.

Carluccio A, Contri A, Gloria A, Veronesi MC, Sfirro MP, Parrillo S, Robbe D. (2017): Correlation between some arterial and venous blood gas parameters in healthy newborn Martina Franca donkey foals from birth to 96 hours of age. Theriogenology 87, 173–178.

Colella M, Biran V, Baud O (2016): Melatonin and the newborn brain. Early Human Development 102, 1–3.

Cordoba R, Pkiyach S, Rooke JA, Edwards SA, Penny PC, Pike I (2000): The effect of feeding salmon oil during pregnancy on causes of piglet deaths prior to weaning. Proceedings of the British Society of Animal Science. Abstract 105.

Cruz RKS, Alfonso A, Souza FF, Oba E, Padovani CR, Ramos PRR, Lourenco MLG, Chiacchio SB (2017): Evaluation of neonatal vitality and blood glucose, lactate and cortisol concentrations in foals of the Paint Horse breed. Pesquisa Veterinária Brasileira 37, 891–896.

de Camargo Ferraz G, Teixeira-Neto AR, de Freitas D´Angelis FH, de Lacerda-Neto JC, de Queiroz-Neto A (2006): Long-term creatine supplementation improves the aerobic capacity of horses. Ciência Rural 36, 514–519.

De Cramer KGM, Joubert KE, Nothling JO (2017): Puppy survival and vigor associated with the use of low dose medetomidine premedication, propofol induction and maintenance of anesthesia using sevofluorane gas-inhalation for cesarean section in the bitch. Theriogenology 96, 10–15.

Declerck I, Dewulf J, Decaluwe R, Maes D (2016): Effects of energy supplementation to neonatal (very) low birth weight piglets on mortality, weaning weight, daily weight gain and colostrum intake. Livestock Science 183, 48–53.

Dickinson H, Ellery S, Ireland Z, LaRosa D, Snow R, Walker DW (2014): Creatine supplementation during pregnancy: summary of experimental studies suggesting a treatment to improve fetal and neonatal morbidity and reduce mortality in high-risk human pregnancy. BMC Pregnancy Childbirth 27, 14–150.

Dutra F, Banchero G (2011): Polwarth and Texel ewe parturition duration and its association with lamb birth asphyxia. Journal of Animal Science 89, 3069–3078.

Dwyer CM (2008): The welfare of the neonatal lamb. Small Ruminant Research 76, 31–41.

Ellery SJ, Dickinson H, McKenzie M, Walker DW (2016): Dietary interventions designed to protect the perinatal brain from hypoxic-ischemic encephalopathy – Creatine prophylaxis and the need for multi-organ protection. Neurochemistry International 95, 15–23.

Endesfelder S, Weichelt U, Strauss E, Schlor A, Sifringer M, Scheuer T, Buhrer C, Schmitz T (2017): Neuroprotection by caffeine in hyperoxia-induced neonatal brain injury. International Journal of Molecular Sciences, doi: 10.3390/ijms18010187.

Figueira RL, Goncalves FL, Simoes AL, Bernardino CA, Lopes LS, Castro e Silva O, Sbragia L (2016): Brain caspase-3 and intestinal FABP responses in preterm and term rats submitted to birth asphyxia. Brazilian Journal of Medical and Biological Research, doi: 10.1590/1414-431X20165258.

https://doi.org/10.17221/86/2018-VETMED

Filippi L, Fiorini P, Daniotti M, Catarzi S, Savelli S, Fonda C, Bartalena L, Boldrini A, Giampietri M, Scaramuzzo R, Papoff P, Del Balzo F, Spalice A, la Marca G, Malvagia S, Della Bona ML, Donzelli G, Tinelli F, Cioni G, Pisano T, Falchi M, Guerrini R (2012): Safety and efficacy of topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia (NeoNATI). BMC Pediatrics, doi: 10.1186/1471-2431-12-144.

Fix JS, Cassady JP, Holl JW, Herring WO, Culbertson MS, See MT (2010): Effect of piglet birth weight on survival and quality of commercial market swine. Livestock Science 132, 98–106.

Gonzalez-Bulnes A, Astiz S, Ovilo C, Lopez-Bote CJ, Torres-Rovira L, Barbero A, Ayuso M, Garcia-Contreras C, Vazquez-Gomez M (2016): Developmental origins of health and disease in swine: implications for animal production and biomedical research. Theriogenology 86, 110–119.

Gonzalez-Lozano M, Mota-Rojas D, Velazquez-Armenta EY, Nava-Ocampo AA, Hernandez-Gonzalez R, Becerril-Herrera M, Trujillo-Ortega ME, Alonso-Spilsbury M (2009a): Obstetric and fetal outcomes in dystocic and eutocic sows to an injection of exogenous oxytocin during farrowing. Canadian Veterinary Journal 50, 1273–1277.

Gonzalez-Lozano M, Ortega MET, Becerril-Herrera M, Alonso-Spilsbury M, Ramirez-Necoechea R, Hernandez-Gonzalez R, Mota-Rojas D (2009b): Effects of oxytocin on critical blood variables from dystocic sows (in Spanish). Veterinaria México 40, 231–245.

Gonzalez-Lozano M, Trujillo-Ortega ME, Alonso-Spilsbury M, Rosales AM, Ramirez-Necoechea R, Gonzalez-Maciel A, Martinez-Rodriguez R, Becerril-Herrera M, Mota-Rojas D (2012): Vetrabutine clorhydrate use in dystocic farrowings minimizes hemodynamic sequels in piglets. Theriogenology 15, 455–461.

Herpin P, Le Dividich J, Hulin JC, Fillaut M, De Marco F, Bertin R (1996): Effects of the level of asphyxia during delivery on viability at birth and early postnatal vitality of newborn pigs. Journal of Animal Science 74, 2067–2075.

Herpin P, Hulin JC, Le Dividich J, Fillaut M (2001): Effect of oxygen inhalation at birth on the reduction of early postnatal mortality in pigs. Journal of Animal Science 79, 5–10.

Herrera-Marschitz M, Neira-Pena T, Rojas-Mancilla E, Espina-Marchant P, Esmar D, Perez R, Munoz V, Gutierez-Hernandez M, Rivera B, Simola N, Bustamante D, Morales P, Gebicke-Haerter PJ (2014): Perinatal asphyxia: CNS development and deficits with delayed onset. Frontiers in Neuroscience, doi: 10.3389/fnins.2014.00047.

IMSS-632-13 (n.d.): Clinical Practice Guideline (GPC): Diagnosis and treatment of neonatal asphyxia. Mexican Social Security Institute. Medical Benefits Direction (México D.F.), 1–21.

Ireland Z, Dickinson H, Snow R, Walker DW (2008): Maternal creatine: does it reach the fetus and improve survival after an acute hypoxic episode in the spiny mouse (Acomys cahirinus)? American Journal of Obstetrics & Gynecology 198, 431.e1–6.

Jimenez-Bravo MA, Mota-Rojas D, Orozco-Gregorio H, Perez-Guille B, Soriano-Rosales R, Roldan-Santiago P, Alonso-Spilsbury M, Arch-Tirado E, Mora-Medina P, Martinez-Burnes J (2016): Evaluation of the protective effect of thiamine pyrophosphate base don the biochemical analysis of rabbit foetuses at 30 days of gestation. Reproductive Toxicology 65, 359–364.

Katz L (2006): Perinatal asphyxia syndrome in a quarter horse foal. Veterinary Clinics of North America: Equine Practice 22, 193–208.

Knottenbelt DC, Holdstock N, Madigan JE (2004): Equine Neonatology: Medicine and Surgery. Elsevier, Philadelphia. 508 pp.

Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, Candow DG, Kleiner SM, Almada AL, Lopez HL (2017): International society of sports nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. Journal of International Society of Sports Nutrition, doi: 10.1186/s12970-017-0173-z.

Lee M, McGeer EG, McGeer PL (2016): Quercetin, not caffeine is a major neuroprotective component in coffee. Neurobiology of Aging 46, 113–123.

Lu KG, Barr BS, Embertson R, Schaer BD (2006): Dystocia-A true equine emergency. Clinical Techniques in Equine Practice 5, 145–153.

Marseglia L, D´Angelo G, Manti S, Reiter RJ, Gitto E (2016): Potential utility of melatonin in preeclampsia, intrauterine fetal growth retardation, and perinatal asphyxia. Reproductive Sciences 23, 970–977.

Martz P, Georgiev P, Wehrend A (2017): Prolonged second stage labour and consequences of hypoxia in the neonate: A review. Bulgarian Journal of Veterinary Medicine, doi: 10.15547/bjvm.2012.

Mellor DJ, Stafford KJ (2004): Animal welfare implications of neonatal mortality and morbidity in farm animals. The Veterinary Journal 168, 118–133.

Miller SL, Yan EB, Castillo-Melendez M, Jenkin G, Walker DW (2005): Melatonin provides neuroprotection in the late-gestation fetal sheep brain in response to umbilical cord occlusion. Developmental Neuroscience 27, 200–210.

Moallem U, Zachut M (2012): The effects of supplementation of various n-3 fatty acids to late-pregnant dairy cows on plasma fatty acid composition of the newborn calves. Journal of Dairy Science 95, 4055–4058.

Mota-Rojas D, Martinez-Burnes J, Trujillo ME, Lopez A, Rosales AM, Ramirez R, Orozco H, Merino A, Alonso-

https://doi.org/10.17221/86/2018-VETMED

Spilsbury M (2005): Uterine and fetal asphyxia monitoring in parturient sows treated with oxytocin. Animal Reproduction Science 86, 131–141.

Mota-Rojas D, Trujillo-Ortega Ma E, Villanueva-Garcia D, Gonzalez-Lozano M, Orozco-Gregorio H, Ramirez-Necoechea R, Olmos-Hernandez A, Alonso-Spilsbury M (2006): Can uterotonics reduce fetal and newborn piglet mortality by perinatal asphyxia and improve functional vitality? Journal of Medical Sciences 6, 884–893.

Muns R, Nuntapaitoon M, Tummaruk P (2016): Non-infectious causes of pre-weaning mortality in piglets. Livestock Science 184, 46–57.

Murray CF, Leslie KE (2013): Newborn calf vitality: Risk factors, characteristics, assessment, resulting outcomes and strategies for improvement. The Veterinary Journal 198, 322–328.

Murray CF, Veira DM, Nadalin AL, Haines DM, Jackson ML, Pearl DL, Leslie KE (2015): The effect of dystocia on physiological and behavioral characteristics related to vitality and passive transfer of immunoglobulins in newborn Holstein calves. Canadian Journal of Veterinary Research 79, 109–119.

Natarajan G, Lulic-Botica M, Aranda JV (2007): Pharmacology review: Clinical pharmacology of caffeine in the newborn. NeoReviews 8, 214–221.

Nemeth J, Toth-Szuki V, Varga V, Kovacs V, Remzso G, Domoki F (2016): Molecular hydrogen affords neuroprotection in a translational piglet model of hypoxic-ischemic encephalopathy. Journal of Physiology and Pharmacology 67, 677–689.

Nogueira CEW, Lins LA (2010): Equine Neonatology and Pediatrics. Editora e Gráfica Universitária da UFPel, Rio Grande do Sul, Brazil.

Ohl F, van der Staay FJ (2012): Animal welfare: at the interface between science and society. Veterinary Journal 192, 13–19.

Olmos-Hernandez A, Trujillo-Ortega ME, Alonso-Spilsbury M, Sanchez-Aparicio P, Ramirez-Necoechea R, Mota-Rojas D (2008): Foetal monitoring, uterine dynamics and reproductive performance in spontaneous farrowings in sows. Journal of Applied Animal Research 33, 181–185.

Onatibia-Astibia A, Martinez-Pinilla E, Franco R (2016): The potential of methylxanthine-based therapies in pediatric respiratory tract diseases. Respiratory Medicine 112, 1–9.

Orozco-Gregorio H, Bonilla-Jaime H, Mota-Rojas D, Trujillo-Ortega ME, Roldan-Santiago P, Martinez-Rodriguez R, Borderas-Tordesillas F, Flores-Peinado S, Mora-Medina P, Ramirez-Necoechea R (2012): Effects of subcutaneous administration of caffeine on the physiometabolic profile of low-birthweight neonate piglets. Animal Production Science 52, 981–990.

Orozco-Gregorio H, Mota-Rojas D, Alonso-Spilsbury M, Olmos-Hernandez A, Ramirez-Necoechea R, Velazquez-Armenta EY, Nava-Ocampo AA, Hernandez-Gonzalez R, Trujillo-Ortega ME, Villanueva-Garcia D (2008): Short-term neurphysiologic consequences of intrapartum asphyxia in piglets born by spontaneous parturition. International Journal of Neuroscience 118, 1299–1315.

Orozco-Gregorio H, Mota-Rojas D, Bonilla-Jaime H, Trujillo-Ortega ME, Becerril-Herrera M, Hernandez-Gonzalez R, Villanueva-Garcia D (2010): Effects of administration of caffeine on metabolic variables in neonatal pigs with peripartum asphyxia. American Journal of Veterinary Research 71, 1214–1219.

Orozco-Gregorio H, Mota-Rojas D, Villanueva D, Bonilla-Jaime H, Suarez-Bonilla X, Torres-Gonzalez L, Bolanos D, Hernandes-Gonzalez R, Martinez-Rodriguez R, Trujillo-Ortega ME (2011): Caffeine therapy for apnoea of prematurity: Pharmacological treatment. African Journal of Pharmacy and Pharmacology 5, 564–571.

Park HW, Lim G, Chung SH, Chung S, Kim KS, Kim SN (2015): Early caffeine use in very low birth weight infants and neonatal outcomes: A systematic review and meta-analysis. Journal of Korean Medical Science 30, 1828–1835.

Perez-de-Sa V, Cunha-Goncalves D, Nordh A, Hansson S, Larsson A, Ley D, Fellman V, Werner O (2009): High brain tissue oxygen tension during ventilation with 100% oxygen after fetal asphyxia in newborn sheep. Pediatric Research 65, 57–61.

Perrone S, Bracciali C, Di Virgilio N, Buonocore G (2017): Oxygen use in neonatal care: A two-edged sword. Frontiers in Pediatrics, doi: 10.3389/fped.2016.00143.

Petzold M, Meyer U, Kersten S, Breves G, Daenicke S (2014): Feeding conjugated linoleic acids and various concentrate proportions to late pregnant cows and its consequence on blood metabolites of calves. Livestock Science 161, 95–100.

Pirrone A, Panzani S, Govoni N, Castagnetti C, Veronesi MC (2013): Thyroid hormone concentrations in foals affected by perinatal asphyxia syndrome. Theriogenology 80, 624–629.

Probo M, Giordano A, Moretti P, Opsomer G, Fiems LO, Veronesi MC (2012): Mode of delivery is associated with different hematological profiles in the newborn calf. Theriogenology 77, 865–872.

Quiniou N, Dagorn J, Gaudre D (2002): Variation of piglets birth weight and consequences on subsequent performance. Livestock Production Science 78, 63–70.

Retes-Lopez R, Martin-Rivera M, Ibarra-Flores F, Moreno-Medina S, Denogean-Ballesteros FG (2013): Analysis of profitability of beef calves in Sonora (in Spanish). Revista Mexicana de Agronegocios 33, 588–598.

https://doi.org/10.17221/86/2018-VETMED

Robertson NJ, Faulkner S, Fleiss B, Bainbridge A, Andorka C, Price D, Powell E, Lecky-Thompson L, Thei L, Chandrasekaran M, Hristova M, Cady EB, Gressens P, Golay X, Raivich G (2013): Melatonin augments hypothermic neuroprotection in a perinatal asphyxia model. Brain 136, 90–105.

Robertson SM, Friend MA, Doran GS, Edwards S (2018): Caffeine supplementation of ewes during lambing may increase lamb survival. Animal 12, 376–382.

Rooke JA, Sinclair AG, Ewen M (2001): Changes in piglet tissue composition at birth in response to increasing maternal intake of long-chain n-3 polyunsaturated fatty acids are non-linear. British Journal of Nutrition 86, 461–470.

Seddon YM, Cain PJ, Guy JH, Edwards SA (2013): Development of a spreadsheet based financial model for pig producers considering high welfare farrowing systems. Livestock Science 157, 317–321.

Sicilia-Argumedo G, Martinez-Avila MA, Valenzuela-Peraza A, Gonzalez-Zavala MA, Granados-Rojas L, Barragan-Mejia MG (2007): Protective effect of thiamine pyrophosphate in the hippocampus of rats exposed to stress by forced immobilization. Veterinaria México 38, 429–438.

Skouroliakou M, Bacopoulou F, Markantonis SL (2010): Caffeine versus theophylline for apnea of prematurity: A randomised controlled trial. Journal of Paediatrics and Child Health 45, 587–592.

Smith BP (2002): Large Animal Internal Medicine. 3rd edn. Manole, São Paulo. 1728 pp.

Sullivan PG, Geiger JD, Mattson MP, Scheff SW (2000): Dietary supplement creatine protects against traumatic brain injury. Annals of Neurology 48, 723–729.

Superchi P, Mazzoni C, Zanardelli P, Piancastelli C, Zambini EM, Beretti V, Sabbioni A (2013): Effects of oral caffeine administration to sows with induced parturition on hypoxia in piglets. Livestock Science 157, 372–377.

Superchi P, Saleri R, Farina E, Cavalli V, Riccardi E, Sabbioni A (2016): Effects of oral administration of caffeine on some physiological parameters and maternal behaviour of sows at farrowing. Research in Veterinary Science 105, 121–123.

Tollofsrud PA, Medbo S, Solas AB, Drevon CA, Saugstad OD (2002): Albumin mixed with meconium attenuates pulmonary dysfunction in a newborn piglet model with meconium aspiration. Pediatric Research 52, 545–553.

Tonnessen R, Sverdrup Borge K, Nodtvedt A, Indrebo A (2012): Canine perinatal mortality: A cohort study of 224 breeds. Theriogenology 77, 1788–1801.

Trujillo-Ortega ME, Mota-Rojas D, Olmos-Hernandez A, Alonso-Spilsbury M, Gonzalez M, Orozco H, Ramirez-Necoechea R, Nava-Ocampo AA (2007): A study of piglets born by spontaneous parturition under uncontrolled conditions: could this be a naturalistic model for the study of intrapartum asphyxia? Acta Biomedica 78, 29–35.

Valenzuela-Peraza A, Martinez-Avila MA, Jimenez Bravo-Luna MA, Granados-Rojas L, Mendoza-Torreblanca JG, Barragan-Mejia MG (2014): Thiamine pyrophosphate reduces hypoxia-induced cellular damage in neonatal rat brain. International Journal of Morphology 32, 531–536.

Vanderhaeghe C, Dewulf J, de Kruif A, Maes D (2013): Non-infectious factors associated with stillbirth in pigs: a review. Animal Reproduction Science 139, 76–88.

Vento M, Sastre J, Asensi MA, Vina J (2005): Room-air resuscitation causes less damage to heart and kidney tan 100% oxygen. American Journal of Respiratory and Critical Care Medicine 172, 1393–1398.

Veronesi MC, Panzani S, Faustini M, Rota A (2009): An Apgar scoring system for routine assessment of newborn puppy viability and short-term survival prognosis. Theriogenology 72, 401–407.

Welin AK, Svedin P, Lapatto R, Sultan B, Hagberg H, Gressens P, Kjellmer I, Mallard C (2007): Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. Pediatric Research 61, 153–158.

WHO – World Health Organization (2017): Reduce the mortality of newborns. Descriptive Note, October 2017. Available at www.who.int/mediacentre/factsheets/fs333/es/ (Accessed: January 22, 2018).

Wilkins PA (2003): Acute respiratory failure: Diagnosis, monitoring techniques, and therapeutics. Clinical Techniques in Equine Practice 2, 56–66.

Xu L, Dong W, Zhao J, Xu Y (2015): Effect of marine collagen peptides on physiological and neurobehavioral development of male rats with perinatal asphyxia. Marine Drugs 13, 3653–3671.

Yadegari M, Khazaei M, Anvari M, Eskandari M (2016): Prenatal caffeine exposure impairs pregnancy in rats. International Journal of Fertility & Sterility 9, 558–562.

Yeates JW, Main DC (2008): Assessment of positive welfare: a review. Veterinary Journal 175, 293–300.

Yli BM, Kjellmer I (2016): Pathophysiology of foetal oxygenation and cell damage during labour. Best Practice & Research Clinical Obstetrics & Gynaecology 30, 9–21.

Zaleski HM, Hacker RR (1993): Variables related to the progress of parturition and probability of stillbirth in swine. Canadian Veterinary Journal 34, 109–113.

Received: June 12, 2018
Accepted after corrections: March 4, 2019