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Caffeine administered to pregnant sows improves piglet vitality, gas exchange and body weight gain

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ABSTRACT

Intra-partum asphyxia is the most common non-infectious etiology limiting the performance of neonate piglets. Previous studies indicate caffeine (orally and subcutaneously) reverses the effects of intra-partum asphyxia in neonate piglets. In this study, there was investigation of whether use of a novel therapeutic protocol for administering caffeine subcutaneously to pregnant sows would improve the newborn piglets' vitality, physio-metabolic profiles and body weight gain. Sows were randomly divided into two groups ($n = 10$ each). Caffeine or NaCl 0.9% was administered 2 days pre-farrowing. Physio-metabolic profiles were measured using blood from the anterior vena cava. The vitality of piglets was evaluated immediately after birth. Piglets ($n = 180$) were weighed at birth and on days 7, 14 and 21 of lactation. Caffeine positively affected the vitality of the piglets, as indicated by greater vitality scores than that for the control group (8.72 ± 0.12 compared with 7.28 ± 0.16, $P < 0.001$). Metabolic values were similar between groups, but pO_2 values were greater in the piglets with greater vitality scores treated with caffeine (19.10 ± 0.82 compared with 14.49 ± 1.42, $P < 0.01$), indicating increased respiratory rates. Body weight gain at day 21 was greater in the piglets treated with caffeine that had greater vitality scores than the control piglets having greater vitality scores (6.87 ± 0.18 compared with 6.52 ± 0.25 kg, $P < 0.05$). Caffeine administration before birth improves the vitality and respiratory capacity of piglets, increasing their adaptation to extra-uterine environment.

1. Introduction

For decades, neonatal mortality has constituted a serious health problem in the swine production industry worldwide. Intra-partum asphyxia is the major non-infectious cause of stillbirth piglets, newborn piglet deaths within the first 72 h post-birth, and is

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responsible for 10%–20% of pre-weaning deaths (Baxter et al., 2011; Muns et al., 2016). There are reports that asphyxia during parturition also results in a decreased viability and subsequent growth rate of surviving neonates (van Wettere et al., 2018). At the time of farrowing, 14% of liveborn piglets have sub-optimal vitality, less than optimal blood flow, and poor fetal oxygenation (Mota-Rojas et al., 2012). Furthermore, fetuses commonly have intermittent periods of mild hypoxia due to uterine contractions and the mechanical pressure inherent to the birth process (Yli and Kjellmer, 2016). Hypoxia, however, results in asphyxia only if feto-maternal blood gas exchange is altered, because this leads to hypoxemia, hypercapnia, ischemia and metabolic acidosis (Barkhuizen et al., 2017). Also, certain characteristics of piglets – such as umbilical cord integrity, birth order in the litter, and neonatal weight affect intra-partum asphyxia (Baxter et al., 2011). Thus, therapeutic strategies designed to prevent and/or treat this condition are important for improving the efficiency of pork production in swine enterprises.

The respiratory effects of caffeine are well-known (Park et al., 2015). Caffeine is apparently and antagonist at adenosine receptors which leads to enhancement of the piglets' capacity to adapt to their post-uterine environment after birth (Superchi et al., 2013). In previous studies, there was assessment of the effect of 35 mg of caffeine (administered orally and subcutaneously) on blood pO_2, pCO_2, glucose, lactate concentrations as well as pH in neonatal pigs with peripartum asphyxia (Orozco-Gregorio et al., 2010, 2012), establishing that caffeine treatments lead to improvements in physio-metabolic profiles and the vitality of neonatal piglets. Interestingly, these beneficial effects were observed only in neonates that weighed more than 1.100 kg at birth. In contrast, treatment with caffeine decreased postpartum performance in piglets with lesser neonatal weight by having detrimental effects on body weight gain (Orozco-Gregorio et al., 2012). Superchi et al. (2013, 2016) have reported that there is a decrease in the incidence of stillbirths and an increase in the thermoregulatory capacity of piglets when there is caffeine supplementation to the diet of pregnant sows on gestational day 113. There, however, was only evaluation of the behavior of the piglets in this previous study. Because behavioral evaluations are subjective indicators of survival, it is important that physio-metabolic indicators be assessed to obtain more accurate prognoses of piglet survival.

The aim of this study, therefore, was to evaluate a novel therapeutic protocol based on subcutaneous administration of caffeine to pregnant sows that might be used as a routine practice in the prophylactic management of piglet hypoxia.

2. Materials and methods

2.1. Study conditions

Neonatal piglets (n = 180), born to 20 multiparous (3.6 ± 0.32 births; weight: 200–280 kg) Yorkshire-Landrace sows at the Center for Education, Research and Extension in Swine Production (CEIEPP-UNAM) in central Mexico, were used. The sows were housed in individual farrowing crates at 23 ± 2 °C with a standard diet being fed and water being provided *ad libitum*. Sows were randomly divided into two groups of ten animals each: Control (NaCl 0.9%) and Caffeine (Loeffler, Mexico). All births were induced 24 h prior to the probable date of farrowing (day 114) with cloprostenol (1 mL, i.m.) (Bioestrophan, Laboratorios Syva, Querétaro, Mexico). The neonatal piglets received no medical care or therapeutic interventions during the first few minutes after birth so as not cause confounding of treatment effects.

The Internal Committee for the Care and Use of Animals (CICUA) of the Faculty of Veterinary Medicine (UNAM) approved the experimental protocol for the study (Protocol number 062), and all procedures were performed in accordance with established national guidelines.

2.2. Experimental procedures

On gestational days 113 and 114, the sows received a solution of (a) 0.9% sodium chloride (Control), or (b) Caffeine (210 mg/day) subcutaneously in the peri-vulvar area at a volume of 4.2 mL. This dose was calculated following Orozco-Gregorio et al. (2012), based on 35 mg per piglet with an estimated fetal weight of 1.0 kg and an average litter size of 12 piglets. Blood samples were collected from all piglets with no umbilical cord manipulations occurring immediately after birth by puncturing the anterior vena cava with heparinized syringes (23 g x 1" needles). This procedure was performed less than 20 s after birth. Concentrations of glucose (mmol/L), lactate (mmol/L), pH and partial carbon dioxide [pCO_2 (mmHg)] and oxygen [pO_2 (mmHg)] pressure were quantified using a critical blood analysis system (Epocal Inc., Ottawa, Canada). Piglet vitality was quantified using the vitality scale that has been previously described by Orozco-Gregorio et al. (2010).

Cardiac frequency was determined using a stethoscope, and classified as < 110, 121–160 or > 161 beats/min. The interval between birth and the first respiration (the point at which thoracic movements were observed accompanied by exhalation of air) and was classified as occurring ≥ 60 s, 16–59 seconds, and ≤ 15 s. Skin color was classified as pale, cyanotic or pink. The interval between birth and standing while using all four legs was classified as > 5 min, 1–5 minutes, and < 1 min. Meconium staining of the skin was classified as severe, mild or none. A score of 0 (minimum indication of vitality) to 2 (maximum indication of vitality) was assigned for each category and used to obtain an overall vitality score of 0–10 for each neonate.

The inclusion criteria for classifying the piglets was modified from that described by Trujillo-Ortega et al. (2011) using, exclusively, the vitality score obtained regardless of the physio-metabolic profile. All the piglets were immediately classified into two groups: relatively lesser vitality (LV), which included those that had a vitality scale of < 5) to the piglets with scores of 7; and that had a relatively greater vitality (GV), including those with scores of ≥ 8. After evaluating vitality, all the neonates were weighed and returned to the crates with their littermates and dam. Piglets were weighed on days 7, 14 and 21 of lactation.

2.3. Statistical analyses

All statistical analyses were conducted using JMP 8.0 (JMP Institute, Marlow, Buckinghamshire, UK). Descriptive statistics were obtained for all the variables assessed and normality assays were performed. Data that did not have a normal distribution were log-transformed. To assess the effect of treatment and vitality classification on the values for physiological blood variables and body weight, the piglet data were analyzed using the Generalized Linear Mixed Model (PROC GLMM) procedure from JMP 8.0. The physiological blood variables and weight were considered to be the dependent variables, while treatment was the independent variable. The statistical model included the factors of treatment and vitality class, as well as the interaction of values for these two variables, with the sow as a random factor. Sow parity was regarded as a fixed effect. To eliminate confounding factors from the results, the effect of treatment and vitality classification was evaluated in terms of farrowing duration and litter size. Statistical differences among the least square means in all cases were assessed with the significance level set at $\alpha = 0.05$.

3. Results

To establish whether there was confounding of the data due to the sow's parity, there was use of farrowing duration and litter size as variables for comparative analyses. The sow's parity did not affect the vitality of offspring or the duration of farrowing because the durations of parturition were similar for sows with varying numbers of parities. In addition, litter size, determined as the total number of liveborn piglets, was greater ($P < 0.001$) in the sows treated with caffeine (Table 1).

3.1. Vitality scale

The piglets born to the caffeine-treated sows had greater vitality scores than piglets of sows in the control group (8.72 ± 0.12 compared with 7.28 ± 0.16, $P < 0.001$). Based on the vitality scores, the piglets were subsequently sub-classified as having a relatively lesser vitality (LV) or greater vitality (GV). Administration of caffeine to the sows late in pregnancy had a positive effect on the vitality scores of the offspring and there was a lesser number of newborn piglets with the LV score when sows were treated with caffeine compared to piglets from sows in the Control group. Also, caffeine administration resulted in a greater percentage of piglets with a GV score from these dams compared with piglets from the Control group (89.58% compared with 45.88%, $P < 0.001$). The caffeine-treated sows had more liveborn piglets than sows of the Control group ($P < 0.05$), so litter size was greater with fewer stillbirths when sows were treated with caffeine (Table 1).

3.2. Physio-metabolic profiles

All values for the physiometabolic profiles and the interactions with the factors of vitality and sows' parity are included in Table 2. Although sows in both the control and caffeine-treatment groups had piglets with a LV score, pH values for piglets were similar in both sub-groups ($P = 0.37$). It, however, is clear that the piglets from caffeine-treated sows had greater pH values (7.28 and 7.30 for piglets with LV and GV scores, respectively) than the piglets from sows of the Control group (7.23 and 7.30 for piglets with LV and GV scores, respectively). Likewise, glucose values were similar with no significant differences in all the piglets from caffeine-treated sows regardless of their vitality scores ($P = 0.47$). The piglets from sows of the Control group, however, had glucose values of less than 2.22 mmol/L, possibly indicating that these piglets were hypoglycemic. Similarly, there were no differences ($P = 0.10$) in lactate values between the piglets with LV and GV scores, or in the interaction with the factor of treatment.

When the respiratory variables were evaluated, only the piglets with LV scores from the sows treated with caffeine had lesser pCO_2 values (LV: 46.53; GV: 44.35 mm Hg, $P < 0.05$) and greater pO_2 values (LV: 20.62; GV: 19.10 mm Hg, $P < 0.01$) than the piglets from sows of the Control group [pCO_2 (LV: 58.89; GV: 50.24 mm Hg); pO_2 (LV: 17.67; GV: 14.49 mm Hg)].

3.3. Body weight gain

The average piglet weight at birth was similar in both groups (1.410 ± 0.09 and 1.605 ± 0.08 kg, $P = 0.133$, for piglets from sows of the Control and caffeine-treated groups, respectively). When considering piglets having LV and GV scores, birthweights, however, were different ($P < 0.05$) because the piglets from sows treated with caffeine weighed more, regardless of vitality classification than piglets from sows of the Control group. Piglets from sows of both groups had gradual increases in body weight during lactation (Table 3), and by the third week when weaning occurred (day 21), the piglets from sows treated with caffeine had gained more body weight ($P < 0.05$): about 410 g for piglets with a LV score and 350 g for piglets with the GV score, compared to the control group in both vitality classifications (LV and GV control piglets).

4. Discussion

The scores on the vitality scale are associated with the piglets' probability of survival in the postpartum phase because these scores are related to the capacity for piglets to recover from any stress-induced occurrence during parturition (Trujillo-Ortega et al., 2011). The vitality scale results in piglets in the present study may be due to the direct effects of caffeine on the respiratory center because at this center there can be increases of sensitivity to CO_2 when some physiological conditions prevail and there is a resulting respiratory response such as stimulation of diaphragm contractility (Orozco-Gregorio et al., 2011). These findings indicate that most of the

Table 1
Values for variables of the sows and interactions with birth processes.

	Control		Caffeine Treated		Effects				
Variables	Lesser vitality Mean ± EE	Greater vitality Mean ± EE	Lesser vitality Mean ± EE	Greater vitality Mean ± EE	Treatment *P*-value	Vitality *P*-value	Parity *P*-value	Treatment*Vitality *P*-value	Treatment*Parity *P*-value
Duration of farrowing (min)	320.89 ± 25.21 a	325.68 ± 29.81 a	305.06 ± 49.48 a	287.18 ± 17.67 a	0.3947	0.8472	0.7172	0.7217	0.0879
Liveborn piglets	10.4 ± 0.68 ab	9.04 ± 0.66 b	11.80 ± 0.68 ab	11.64 ± 0.49 a	0.0011	0.3884	0.7276	0.3171	0.3081
Litter size	11.72 ± 0.58 b	11.60 ± 0.62 b	12.30 ± 0.59 a	12.60 ± 0.57 a	0.0033	0.4854	0.6256	0.4151	0.4071
Stillbirths	7 (18.42 %)*	6 (16.66%)	3 (12.5 %)	2 (2.77%) **	0.0419	0.3865	0.4153	0.2112	0.3610

Least-squares Mean ± standard error.
[a,b,c]Letters indicate differences between vitality class, vitality and treatment ($P < 0.05$).
(PROC GLMM, JMP 8.0).
* Significant differences ($P = 0.001$).
** Significant differences ($P < 0.05$).

Table 2
Physio-metabolic variables at birth for piglets with relatively lesser and greater vitality piglets depending on treatment and interactions.

Variable	Control		Caffeine Treated		Effects				
	Lesser vitality Mean ± EE	Greater vitality Mean ± EE	Lesser vitality Mean ± EE	Greater vitality Mean ± EE	Treatment *P*-value	Vitality *P*-value	Parity *P*-value	Treatment*Vitality *P*-value	Treatment*Parity *P*-value
pH	7.23 ± 0.02 a	7.30 ± 0.02 a	7.28 ± 0.04 a	7.30 ± 0.01 a	0.3777	0.2117	0.2696	0.4896	0.2354
pCO_2 (mmHg)	58.89 ± 4.55 a	50.24 ± 4.72 a	46.53 ± 7.63 a	44.35 ± 3.27 a	0.0488	0.3624	0.1251	0.481	0.3353
pO_2 (mmHg)	17.67 ± 1.18 ab	14.49 ± 1.42 b	20.62 ± 2.37 ab	19.10 ± 0.82 a	0.0148	0.1473	0.5489	0.59	0.0688
Glucose (mmol/L)	1.99 ± 0.19 a	2.12 ± 0.20 a	2.48 ± 0.33 a	2.31 ± 0.13 a	0.0961	0.9356	0.3174	0.4774	0.2084
Lactate (mmol/L)	4.01 ± 0.34 a	4.42 ± 0.41 a	5.39 ± 0.69 a	4.33 ± 0.24 a	0.1549	0.4945	0.3053	0.1045	0.4118

Least-squares Mean ± standard error.
n = number of piglets evaluated.
[a,b,c]Numbers associated with different superscript letters in the same row indicate differences between vitality class and treatment ($P < 0.05$).
Effects; parity and interaction treatment*vitality ($P < 0.05$).
(PROG GLMM, JMP 8.0) (Tukey, $P = 0.05$).

Table 3
Body weight of the lesser and greater vitality piglets at birth and during lactation.

	Control		Caffeine Treated		Effects		
Body Weight (Kg)	Lesser vitality Mean ± EE	Greater vitality Mean ± EE	Lesser vitality Mean ± EE	Greater vitality Mean ± EE	Treatment *P*-value	Vitality *P*-value	Treatment*Vitality *P*-value
At birth	1.39 ± 0.07 b	1.46 ± 0.07 b	1.58 ± 0.09 ab	1.63 ± 0.05 a	0.0349	0.4615	0.9342
First week	2.45 ± 0.13 a	2.61 ± 0.14 a	2.61 ± 0.17 a	2.81 ± 0.10 a	0.2164	0.1995	0.8974
Second week	4.09 ± 0.17 a	4.69 ± 0.18 a	4.56 ± 0.22 a	4.73 ± 0.12 a	0.1832	0.0519	0.2543
Third week	5.93 ± 0.25 b	6.52 ± 0.25 ab	6.34 ± 0.31 ab	6.87 ± 0.18 a	0.166	0.0490	0.9109

Least-squares Mean ± standard error.
n = number of piglets evaluated.
[a,b,c]Numbers associated with different superscript letters in the same row indicate differences between vitality class and treatment ($P < 0.05$).
Effects; parity and interaction treatment*vitality ($P < 0.05$).
(PROG GLMM, JMP 8.0) (Tukey, $P = 0.05$).

beneficial effects of caffeine result from the antagonistic actions of caffeine at the A_1 and A_{2A} receptors which leads to greater piglet vitality scores and survival rates immediately after birth due to the effects of caffeine on respiration that are modulated by adenosine inhibiting the activity of the respiratory center (Oñatibia-Astibia et al., 2016). These actions and responses as a result of caffeine treatment are related to a critical period during the farrowing process and the first few hours post-farrowing, when most pre-weaning deaths occur (Baxter and Edwards, 2018). In this context, prenatal caffeine administration can improve responses to hypoxia in neonatal piglets possibly due to short-term physio-metabolic or behavioral adaptations to the extra-uterine environment. Caffeine treatments may also lead to a reduction in ischemic brain damage after asphyxia; a condition that compromises piglet performance during lactation (Superchi et al., 2016; Robertson et al., 2018).

After classifying the piglets as having LV or GV scores, the pH data indicated there were similar values for both groups, regardless of treatment. It is important to note that before parturition onset, the normal fetal pH is about 7.35, but there is a decrease to a pH of 7.25 during farrowing. Both of these values are considered normal, but values between 7.25 and 7.20 are sub-normal and require monitoring, while a pH of less than 7.20 indicates there is fetal hypoxia (Garabedian et al., 2017). Pulmonary gas exchange is established during the postpartum period, and the variables involved in this process should transition to normal adult values with the greatest changes occurring within the first few minutes after birth (Orozco-Gregorio et al., 2007). Even though in the results of the present study there was no effect of caffeine treatment of sows on whether piglets were classified with LV or GV scores, the piglets from caffeine-treated sows had values that were considered optimal for pulmonary gas exchange indicating that the caffeine treatment contributed to piglets being in a desirable welfare state and having optimal oxygenation (pH 7.30 and 7.28 for GV and LV, respectively). In contrast, the newborn piglets with LV scores from sows in the Control group had pH values considered sub-normal (pH 7.23), and there were more piglets with GV scores from sows of the Control group with the sub-normal pH values ($n = 46$ compared with $n = 39$). These findings underscore the need for proactive treatment of piglets in ways that avoid detrimental hypoxic effects. The blood samples were collected during the first few seconds after birth with the piglets still being in an apnea state and this may have resulted in treatment effects on pH not yet being evident.

Glucose is considered the major source of energy for newborn piglets because piglets are born with limited energy stores. If the supply of, and requirements for glucose are in balance, the fetus obtains adequate oxygen to metabolize glucose aerobically and transfer the energy required for organ functions (Xie et al., 2016; Yli and Kjellmer, 2016). In the present study, caffeine treatment did not result in any significant change in glucose values; however, the newborn piglets with LV scores from sows of the Control group had glucose values (1.99 ± 0.19 mmol/L) of less than 2.22 mmol/L which indicates these piglets were in a state of hypoglycemia. Although the minimum blood glucose concentration required to maintain normal brain functioning is unknown, it is widely-accepted that brain function is compromised when glucose concentrations are in the range of 1.67 to 2.22 mmol/L (Park et al., 2001). The complications of less than optimal glucose values combined with lesser neonatal vitality can lead to failure to initiate suckling of the dam's nipple for obtaining dietary nutrients. As a consequence, piglets may have deficient passive immunity and sub-optimal nutritional profiles that may be reflected in a lack of capacity to gain body weight during lactation. Also, piglets could be stressed due to hypoglycemia-induced hypothermia, which can lead to piglets being in coma relatively quickly after onset of hypoglycemia (Orozco-Gregorio et al., 2012; Baxter and Edwards, 2018).

When in any tissue, there is sub-optimal oxygen concentrations there is a loss of the capacity for oxidative phosphorylation and a resulting transition from an aerobic to anaerobic metabolic state. In anaerobic conditions, pyruvate is reduced to lactate, leading to an inefficient energy transfer (Yli and Kjellmer, 2016). With the present results, caffeine treatment did not result in a modification in lactate values when there was either piglet vitality classification. It is well-known that greater than optimal lactate concentrations at birth are indicators of hypoxia, but lactate concentrations were within normal limits in all sub-groups of piglets from sows in the Control group in the present study (4.01 ± 0.34 to 4.42 ± 0.41 mmol/L) and in the piglets with GV scores as a result of caffeine treatment of their dams (4.33 ± 0.24 mmol/L). In contrast, the piglets with LV scores from sows treated with caffeine had greater lactate values, though the lactate concentration was not statistically different from those of piglets with GV scores (5.39 ± 0.69 mmol/L, $P = 0.49$). The piglets from caffeine-treated sows that had LV scores had lesser lactate values than those reported by Trujillo-Ortega et al. (2007) for piglets with LV scores and asphyxiated neonates (9.58 ± 3.15 mmol/L). Conversely, in

the present study, during the first seconds after birth there was no difference in pH, glucose or lactate concentrations between piglets with LV and GV scores which indicates energy metabolism does not affect the vitality of piglets, at least in the first few seconds subsequent to birth.

Gas exchange is a fundamental aspect of the physio-metabolic evaluation of newborn piglets because evaluation of this variable is important in assessing the extent of asphyxia during parturition and for predicting neonatal survival (Orozco-Gregorio et al., 2008; Mota-Rojas et al., 2015). In the present study, there was a difference ($P < 0.05$) in pCO_2 concentrations between piglets with LV and GV scores and sow treatment groups because the pCO_2 values for the piglets from caffeine-treated sows were less than those from sows of the Control group when values of pigs with both LV and GV scores were considered. Likewise, the pO_2 concentrations were greater in piglets with LV and GV scores from sows treated with caffeine ($P < 0.05$), a finding that confirms the effect of caffeine administration on increasing respiratory rates, as was reflected in the reduction of pCO_2 and the increase in pO_2 (Orozco-Gregorio et al., 2012). The blood gas values of all the animals were less than those reported in other studies (Trujillo-Ortega et al., 2011; Rootwelt et al., 2013; Mota-Rojas et al., 2015), regardless of the vitality scores [control (pCO2: 58.89 ± 4.55 / 50.24 ± 4.72; pO2: 17.67 ± 1.18 / 14.49 ± 1.42) and caffeine-treated (pCO2: 46.53 ± 7.63 / 44.35 ± 3.27; pO2: 20.62 ± 2.37 / 19.10 ± 0.82) for LV and GV, respectively]. This may be a result of the methodological approach used to sample the newborn piglets because blood was collected from the vena cava, while in other studies there was sampling from the umbilical cord or retro-orbital sinus. Fetal piglet physiology is characterized by several adaptive mechanisms that facilitate the transfer of gases between maternal and fetal circulation to support functions and growth in a less than optimal-oxygen environment. The pO_2 is greater in the maternal than the fetal circulatory system, and this concentration difference facilitates maternal-to-fetal oxygen transfer via diffusion across the placenta (Yli and Kjellmer, 2016). Nonetheless, as half of the venous blood from the umbilical cord passes through hepatic circulation to mix with poorly-oxygenated blood before going to the anterior vena cava and entering pulmonary circulation, samples obtained from the vena cava usually contain less oxygen than samples from other vessels (Guyton and Hall, 2016).

Pre-weaning mortality in piglets as a result of perinatal asphyxia is a significant issue in terms of both pork production enterprise economics and piglet welfare. One of the most important indicators during lactation is body weight gain. Results of studies indicate neonates that have lesser vitality scores and birthweights are at risk of dying because of a lesser capacity to adapt to the extra-uterine environment and have difficulty attaining the body weight necessary for energy requirements to be met. As a result, piglets may fail to suckle the maternal teat (Baxter et al., 2008; Orozco-Gregorio et al., 2012; Declerck et al., 2016). Results of previous studies indicate there is a beneficial effect of administering caffeine to neonatal piglets with symptoms of intra-partum asphyxia. In these previous experiments (Orozco-Gregorio et al., 2010, 2012) there was caffeine administration immediately after birth in proportion to birthweight. The approach in the present study, in contrast, was a prophylactic method in which the caffeine-treated piglets received prenatal treatment as a result of treatment of sows with caffeine.

Birthweight is one of the most important covariates for postnatal survival. In this regard, data from the present study indicate piglet weight at farrowing in the two groups was different ($P < 0.05$); hence, it is speculated that any effect of treatment on birthweight in the present study may have resulted from sampling because there was acute treatment with caffeine in late pregnancy (days 113 and 114 pre-farrowing) after the fetuses were fully-developed physically, so it is unlikely that treatment at that stage would have effects on birthweight. During the first 2 weeks of lactation, piglets from caffeine-treated sows had similar body weights as the piglets from sows of the Control group, however, by the end of the study (day 21) the piglets from caffeine-treated sows that had GV scores had gained approximately 350 g more body weight than the piglets with GV scores from sows of the control group. The findings indicate caffeine treatment results in immediate effects on the vigor of newborn piglets that allows for increased access of piglets to nutrient resources as a result of enhancement of the neonates' capacity to suckle the teat. This is evident because piglet weight gain during the first 10 weeks after birth is affected by the extent of asphyxia during parturition, and suggests long-term effects of the lack of oxygen on post-natal performance (Langendijk et al., 2018) that can have detrimental effects on productivity if not treated promptly.

Greater body piglet weights at day 21 subsequent to birth are important because it is well-established that weaning is a stressful period for piglets and during the early post-weaning period there is weight loss, increases in blood cortisol concentrations, suppression of the immune system, and alterations in behavior (McGlone et al., 2017). From this perspective, one advantage of prenatal treatment with caffeine is that it enhances the capacity for physical activity functions after weaning. This variation in weight increase during lactation is due to piglet vitality at birth; hence, it can be inferred that there are long-term beneficial effects related to neonatal vitality resulting from caffeine-based treatment intervention. The present study did not, however, include post-weaning piglet performance assessments, so further research is required to clarify this effect in later stages of development and/or at later production stages.

5. Conclusion

The results of this study indicate that the prophylactic administration of caffeine to sows in late gestation increases the vitality of neonatal piglets because piglets born to the treated sows were more vigorous at birth due to the broad stimulant effect of caffeine. The piglets born to the caffeine-treated sows had greater gas exchange, presumably due to specific effects on the respiratory system that were reflected in the piglets weekly body weight gain.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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