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Research Article

Effect of a single dose of caffeine in pregnant sows on farrowing behaviour, colostrum composition, piglet vitality and growth

Efeito de uma dose única de cafeína em porcas prenhes sobre o comportamento no parto, a composição do colostro, a vitalidade e o crescimento dos leitões

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ABSTRACT

Caffeine is an alkaloid that reduces perinatal hypoxia by acting on adenosine receptors in respiratory centres, enhancing respiratory capacity and piglet viability. This study aimed to evaluate the effects of acute subcutaneous caffeine administration during late gestation in multiparous sows on farrowing, pain behaviours, colostrum composition, and piglet behaviour during lactation. Sows were randomly assigned to two groups: control (NaCl 0.9%) or caffeine (0.5 g/sow/predicted piglet), with treatments given one day before farrowing. No significant effects were observed on farrowing duration, litter size, live or stillborn piglets, or painful behaviour. Although caffeine did not affect birth weight, piglets from the caffeine group gained 0.92 kg more ($p<0.001$) during weaning, likely due to higher protein concentrations in the colostrum. These findings suggest that a single low dose of caffeine late in gestation can improve neonatal vitality, colostrum quality, and weight gain without negatively affecting the farrowing process.

KEYWORDS: Methylxanthines. Neonatal vitality. Farrowing pain. Preweaning mortality.

RESUMO

A cafeína é um alcaloide que reduz a hipóxia perinatal ao atuar nos receptores de adenosina nos centros respiratórios, melhorando a capacidade respiratória e a viabilidade dos leitões. O objetivo deste estudo foi avaliar os efeitos da administração subcutânea de cafeína durante o final da gestação em porcas multíparas sobre o parto, os comportamentos de dor, a composição do colostro e o comportamento dos leitões durante a lactação. As porcas foram distribuídas aleatoriamente em dois grupos: controle (NaCl 0,9%) ou cafeína (0,5 g/porca/leitão previsto), com tratamentos administrados um dia antes do parto. Não foram observados efeitos significativos na duração do parto, nos leitões vivos ou natimortos ou no comportamento doloroso. Embora a cafeína não tenha afetado o peso ao nascer, os leitões do grupo da cafeína ganharam 0,92 kg a mais ($p<0,001$) durante o desmame, provavelmente devido às concentrações mais altas de proteína no colostro. Esses resultados sugerem que uma única dose baixa de cafeína no final da gestação pode melhorar a vitalidade neonatal, a qualidade do colostro e o ganho de peso sem afetar negativamente o processo de parto.

PALAVRAS-CHAVE: Metilxantinas. Vitalidade neonatal. Dor no parto. Mortalidade pré-desmame.

INTRODUCTION

In production animals, perinatal asphyxia is a leading non-infectious cause of newborn mortality. Stillbirth rates in piglets range from 5% to 10% but can reach up to 14% in highly prolific herds. Most stillborn (> 75%) die during birth due to oxygen insufficiency caused by feto-maternal conditions like umbilical cord constriction, birth order, prolonged farrowing, colostrum availability, maternal care, and neonatal weight (GOURLEY et al. 2020, LANGENDIJK & PLUSH 2019, SÁNCHEZ-SALCEDO et al. 2019a, SWINBOURNE et al. 2021). Asphyxia compromises piglet vitality and their ability to adapt to the environment outside the womb, hindering weight gain necessary for energy needs (SÁNCHEZ-SALCEDO et al. 2019b).

Increased litter sizes in commercial sows intensify competition during nursing, potentially compromising preweaning growth and causing early lactation deaths; more than 25% of piglets may not survive to weaning (SCHMITT et al. 2019, GOURLEY et al. 2020). This ongoing issue reflects economic concerns and poor welfare standards, with minimal improvement in practices over decades (BAXTER & EDWARDS 2024). Consequently, effective strategies are needed to support neonates during the transition to postnatal life and enhance survival rates, particularly for less viable piglets (SWINBOURNE et al. 2021).

One potential therapeutic approach is using methylxanthines like caffeine. Known for its respiratory stimulant properties, caffeine has been used in premature human infants and piglets suffering from oxygen deprivation at birth. Research has shown that caffeine is rapidly absorbed and metabolized in pigs. In a study by CUNNINGHAM (1970) when caffeine was administered as a single oral dose of 1.5 g, plasma levels peaked at five hours, with a subsequent erratic decline the next 32 hours with a biological half-life of 4.7 hours. However, when the same dose (1.5 g) was administered intramuscularly, plasma levels peaked at two hours, with a half-life of 11.4 hours.

In a more recent study MENOZZI et al. (2015) administered a single oral dose of caffeine (25 mg/kg) to sows and detected caffeine in plasma 15 minutes after administration (2.51 ± 1.60 µg/mL). Caffeine concentration peaked at 9.51 ± 1.17 hours (Cmax = 20.02 ± 1.51 µg/mL) and showed a biphasic decline pattern. Caffeine has shown promise in improving various physiological functions in animals, such as respiratory and thermoregulatory functions, reducing stillbirth rates, and improving litter size and milk production in sows and ewes. Furthermore, since caffeine freely crosses the placenta, reaching similar levels in fetal and maternal blood, this information is consistent with a previous study in which oral administration of caffeine to sows the day before farrowing improved the vitality of newborn piglets (LI & HACKER 1995, SUPERCHI et al. 2016, DEARLOVE et al. 2018, SWINBOURNE et al. 2021).

Recent studies suggest that administering low doses of caffeine to sows shortly before expected farrowing improves piglet oxygenation, vitality at birth, and subsequent weaning weights (SÁNCHEZ-SALCEDO et al. 2019b). However, the long-term impacts of intrapartum asphyxia remain significant, potentially affecting piglet health for up to 10 weeks post-farrowing (LANGENDIJK & PLUSH 2019), while in the case of the farrowing process, the use of this alkaloid has not been accompanied by an evaluation of the impact this may have on the sow, as it is known that caffeine can

interact in vitro with prostaglandin F2α (PGF2α), increasing uterine contractions, possibly making farrowing uncomfortable or even more painful (DEARLOVE et al. 2018).

Therefore, the aim of this study was to evaluate the subcutaneous administration of a single dose of caffeine (0.5 g/sow/predicted piglet) in the peri-vulvar area of multiparous sows one day before expected farrowing, assessing its effects on farrowing progression, sow behaviors associated with pain, colostrum composition (fat, protein, and carbohydrate), as well as piglet lactation progression, including weight gain, postpartum vitality, and preweaning survival rates.

MATERIALS AND METHODS

Ethics approval

All animals used in this study were kept according to the Mexican legislations. The study protocol was approved by the Bioethics Committee of the Academic Program in Agricultural and Livestock Development of Universidad Veracruzana approved the experimental protocol for the study (MDA-BIO-002) and obeyed the guidelines for the ethical use of animals in applied ethological studies (SHERWIN et al. 2003).

Study conditions

The experimental procedure was carried out from May to July 2022 on a smallholder pig farming in the municipality of Emiliano Zapata in the central zone of the state of Veracruz, Mexico (19°27′27.58″ N, 96°45′57.02″ W, at 940 m.a.s.l.). A total of 163 piglets from 12 sows divided into two groups of 6 sows each [Control (NaCl 0.9%) and Caffeine (Loeffler, Mexico)] were used. All sows were of hybrid genetics (Semen Cardona) 3.33 ± 0.33 parity, BCS: 3 and with a previous litter size average of 13.5 ± 1 piglets) and were housed in individual farrowing crates (1.5 wide X 2.2 long) one week before the probable farrowing date at 30.0 ± 1.0 ºC with a standart diet (13% protein, 3.2 Mcal ME/kg and 18.6 g/d of lysine) being fed and water being provided ad libitum. No farrowing was induced to prevent confounding treatment effects, while piglets received routine farm management at birth and during lactation.

EXPERIMENTAL PROCEDURES

Farrowing process and colostrum omposition

During day 114 of gestation (one day before the probable farrowing date) between 08:00 y 09:00 h, all sows in both groups received subcutaneously in the peri-vulvar area a volume of: a) 5 ml of NaCl 0.9% solution (control) or b) 5 ml of caffeine solution (0.5 g of caffeine, Loeffler, Mexico) according to the dose suggested by our previous study (SÁNCHEZ-SALCEDO et al. 2019b) based on 35 mg per piglet with an average fetal weight of 1.0 kg each and litters of approximately 14 piglets in hyperprolific sows.

At the end of the farrowing process, variables such as its duration, the number of piglets born alive and stillborn were evaluated. All piglets were weighed after farrowing and returned to their crate with their mother to consume colostrum. Subsequently, colostrum samples were collected within 6 h of parturition via milking by hand after the administration of 1 ml of oxytocin intramuscularly (20 UI/ml, Fetol plus, Laboratorios Andoci, S.A. México) and frozen at -20 °C for further analysis of lipids, proteins and carbohydrates by ultrasonic milk analyzer (Lactoscan MCC30, Milkotronic, Bulgaria).

All samples were analyzed in triplicate.

Neonatal vitality and preweaning mortality

Neonatal vitality was assessed at the litter level 24 h postpartum by a trained observer according to the four-point scoring scheme proposed by SCHODL et al. (2019). This scheme allows categorizing the litter according to the number of piglets showing signs of reduced vitality (piglets appear weak, languid, pale, and show reduced activity and insufficient suckling), where vitality score 1) is defined as more than 4 piglets in the litter showing signs of reduced vitality; 2) 3 to 4 piglets in the litter show signs of reduced vitality; 3) 1 to 2 piglets in the litter show signs of reduced vitality and 4) no piglet shows signs of reduced vitality. At the end of the lactation period (21 days postpartum), preweaning mortality was calculated by dividing the number of piglets dead until weaning by the number born alive by 100 (SCHODL et al. 2019). Subsequently, all piglets were weighed, weaned, ear-tagged and moved to the weaning area, where they were grouped with piglets from other litters based on their weight, as is routinely done on the farm.

Pain scale

Sow behaviour during farrowing was monitored by closed-circuit television (CCTV) cameras mounted directly above each farrowing pen; digital video recordings were collected and stored for later study. Measurement was performed using a combination of focal and scan sampling. According to the methodology proposed by ISON et al. (2016), sows were continuously observed 2 min before and 2 min after the expulsion of each piglet, from the first piglet until the birth of the last piglet (farrowing), to finally obtain the total of the frequencies observed throughout farrowing during expulsion. The ethogram of the observed behaviours is presented in Table 1.

Table 1. Ethogram of behaviours observed during the study.

Behaviour	Description
Lie lateral	Lying on one side with udder exposed
Back leg forward	In a lateral lying position, the back leg is pulled forward and/or in towards the body.
Back arch	In a lateral lying position, one or both sets of legs become tense and are pushed away from the body and/or inwards towards the center, forming an arch in the back.
Tail flick	Tail is moved rapidly up and down.

Statistical methods

For production-related variables, such as piglet weight at weaning, farrowing duration, and parity, a multiple linear regression model was applied. The data were analyzed using the statistical package Rstudio (version 1.2.1335), and the model incorporated predictors like treatment, farrowing duration, and parity. This model allowed for the prediction of piglet weight at weaning, explaining 18 % of the variance (R^2= 0.18). The selection of the best model was guided by the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BAI), ensuring the most appropriate fit for the data. These analyses provided insights into how the subcutaneous caffeine administration influenced the production outcomes.

Variables related to colostrum composition, such as fat, protein, and carbohydrate content, were analyzed separately using the independent samples t-test. Since these variables were not included in the regression model, the t-test allowed for

comparison between the groups to assess any significant differences in the colostrum characteristics resulting from the caffeine treatment.

Behavioral data were analyzed based on the the methodology proposed by ISON et al. (2016), which involved detailed behavioral recordings of sows during farrowing and postpartum periods. Given the number of repeated measures and the high correlation between various behavioral variables, Principal Component Analysis (PCA) was employed. PCA helped reduce the complexity of the data by extracting key components through an orthogonal solution, with the components rotated using the Varimax criterion. This technique facilitated the reduction of variables by analyzing the correlation matrix and identifying the main components that contributed to behavioral patterns. The newly derived variables were then subjected to the independent samples t-test to determine if significant behavioral differences existed between the treatment groups.

RESULTS

Farrowing performance and composition of early colostrum

Prepartum caffeine treatment did not affect the duration of farrowing, nor the number of piglets born alive or stillborn compared to the control group (Table 2). Conversely, the multiple linear regression model was statistically significant ($p< 0.001$). In this model, it was identified that caffeine treatment did not affect birth weight; however, it positively predicted weight gain in piglets at weaning ($\beta1std= 0.225$); specifically, there was an increase of (67.2 g) whereas, at longer farrowing duration ($p< 0.0001$) a decrease in piglet weight at weaning was found ($\beta2std= -0.350$); therefore, a decrease of (104.6 g). Additionally, sow parity was statistically significant ($p< 0.001$), with sows that farrowed three times contributing the most significant increase in piglet weaning weights ($\beta3std=0.286$); concretely there was an increase of (85.5 g).

Table 2. Farrowing performance and piglet weight in response to prepartum caffeine treatment.

Variables	Control	Caffeine	*p*-value
Farrowing duration (min)	252 ± 21.31	241 ± 28.07	0.761
Liveborn piglets	13.5 ± 1.05	13.66 ± 2.01	0.943
Stillbirths	0.33 ± 0.21 (0.40 %)	0.16 ± 0.16 (0.19 %)	0.549
Birthweight	1.32 ± 0.15	1.42 ± 0.15	0.620
Weaning weight	4.65 ± 0.15	5.57 ± 0.15	<0.001

Mean ± SEM are shown.

Regarding the composition of colostrum, the concentration of fat and lactose during the first 12 hours postpartum was not influenced by caffeine treatment. However, compared to sows in the control group, the content of colostral protein was significantly higher in caffeine-treated sows (Table 3).

Table 3. Composition of colostrum in caffeine-treated vs control sows.

Variables (%)	Control	Caffeine	*p*-value
Fat	6.22 ± 0.81	4.46 ± 0.83	0.073
Lactose	10.69 ± 0.84	12.54 ± 0.42	0.078
Protein	7.07 ± 0.51	8.37 ± 0.28	0.050

Mean ± SEM are shown.

Litter vitality and preweaning survival

Litters born to untreated sows showed a significantly lower vitality scale score (3.0 ± 0.00) compared to those litters from caffeine-treated sows (3.67 ± 0.21, $p < 0.05$). Consistently, piglet survival was affected by caffeine treatment during lactation since at day 21, the preweaning mortality rate was 13.50 % (11 deaths) for untreated piglets. In contrast, for those exposed to caffeine in utero, it was 4.80 % (4 deaths).

Behavioural indicators of pain in periparturient sows

PCA generated two principal components with eigenvalues exceeding 1.5. These principal components explained a total of 72 % of the total variance. The first principal component (covering 52.74 % of the variance), in which the behavioural measurements are included, had positive factor loadings around 0.4 (Before expulsion: lie lateral and back arch; After expulsion: Lie lateral), and this factor was characterized as potential pain indicators. The second component (explaining 20.20 % of the variance) had negative factor loadings around 0.4 (After expulsion: Back arch and Tail flick) (Table 4). However, no differences due to caffeine treatment were identified in the first ($p = 0.85$) and second component ($p = 0.49$).

Table 4. Principal Component Analysis. Loadings for the records of 4 behaviours pain indicators. Loadings greater than 0.4 are bolded and were used to define the indexes identified in the analysis.

Time period	Behaviour	Component 1	Component 2
Before expulsion	Lie lateral	**0.40**	0.17
	Back leg forward	0.37	0.37
	Back arch	**0.43**	-0.02
	Tail flick	0.32	-0.22
After expulsion	Lie lateral	**0.43**	0.11
	Back leg forward	0.24	**0.45**
	Back arch	0.28	**-0.47**
	Tail flick	0.26	**-0.57**
	% of variance	52.74	20.20

DISCUSSION

In this study, a single low dose of subcutaneous caffeine in the peri-vulvar area administered before farrowing did not affect the duration of farrowing, nor did it influence litter indicators such as the number of live and stillborn piglets. Similarly, the birth weights of piglets were comparable between the caffeine-exposed group and the control group, reflecting the advanced stage of gestation where fetuses are fully developed.

However, at weaning, piglets exposed to prepartum caffeine showed a significant weight increase of 0.920 kg. This contrasts with findings from other studies where higher doses of caffeine (4.8 to 6 g/sow) administered repeatedly (3 days before the predicted farrowing date) or in combination with hormones like progesterone not only reduced birth weights but also decreased weights throughout lactation until weaning (DEARLOVE et al. 2018, VAN WETTERE et al. 2018). This allows us to corroborate our previous findings that showed a significant increase in weaning weight due to the effect of low doses of caffeine (0.5 g/sow/predicted piglet) on the vigorousness of

piglets and their productive performance during lactation (SÁNCHEZ-SALCEDO et al. 2019b).

Additionally, while the factors contributing to successful eutocic farrowing in modern sows remain undefined, it is widely acknowledged that prolonged farrowing diminishes neonatal vitality and piglet viability by exposing them to oxygen-deficient conditions, thereby increasing stillbirth rates (FARMER & EDWARDS 2022, WALLS et al. 2022). Our study showed that longer farrowing durations significantly reduced piglet weaning weights. For hybrid multiparous sows, a farrowing duration of 240 to 300 minutes is considered ideal (JU et al. 2021), with an average duration of 241 minutes observed in caffeine-treated sows in our study.

LANGENDIJK & PLUSH (2019) suggest that sows experiencing prolonged expulsive phases during farrowing are likely compromised before the birth of the first piglet. This extended duration reduces oxygen supply to piglets due to uterine contractions, leading to poor performance not only during farrowing but also post-weaning. This could explain reduced growth rates, as less viable piglets tend to consume less colostrum, a crucial factor influencing growth up to six weeks of age.

In practice, it is well-known that fat sows tend to experience more farrowing problems, which can affect both the sow's welfare and the survival of the piglets. Additionally, sows often repeat the number of piglets born, as well as the number of stillbirths, with these trends typically reflecting a pattern seen across multiple farrowing's (QUESNEL et al. 2008). Sows with more than seven farrowing's are more likely to face complications during farrowing, which can result in an increased incidence of stillbirths (ADI et al. 2022). These factors highlight the importance of closely monitoring sows, especially as they age, to mitigate farrowing difficulties and ensure better outcomes for both the sow and her piglets (WALLS et al. 2022).

In our study, sows with three farrowing's significantly contributed to increased progeny weight at weaning. This finding aligns with previous studies, which suggest that peak reproductive performance and optimal piglet growth are typically observed between the third and fifth farrowing's (NEVRKLA et al. 2021). The combination of caffeine treatment and parity could have enhanced colostrum and milk intake, with adequate colostrum intake being known to improve daily weight gain during lactation and up to weaning. In contrast, sows with fewer parities produced less colostrum, resulting in piglets weaning 10 % lighter than those from multiparous sows, with this difference persisting post-weaning (QUESNEL & FARMER 2019, AMATUCCI et al. 2022).

Although our study did not evaluate colostrum and milk consumption within the litter, previous research suggests that the composition of colostrum from modern hyperprolific sows remains largely unchanged over the last 30 years. Colostrum typically contains high protein concentrations (5-19 %) but low levels of fat (5-7 %) and lactose (5-6 %). Casein constitutes 10-20 % of the total proteins, while the majority (>80 %) is composed of immunoglobulin-rich whey proteins (FARMER et al. 2006, ZHANG et al. 2018, SEGURA et al. 2020, INOUE & TSUKAHARA 2021).

While no statistical differences in fat and lactose were found in our study, we observed notably higher protein levels. Colostrum composition can vary due to factors such as pig breed, diet, hormonal and immune status, stress, and litter characteristics,

particularly birth vitality (QUESNEL & FARMER 2019, INOUE & TSUKAHARA 2021). Interestingly, caffeine treatment significantly increased colostral protein concentration by nearly one percentage point, a result that could be associated with the findings of LI & HACKER (1995), which indicate that caffeine supplementation in pregnant sows (6 g orally from day 60 of gestation to farrowing) improves mammary gland development, increasing mammary epithelial cell count and size, hormonal response, and milk production by 40 % on the first day of lactation compared to controls.

However, the difference in treatment duration between this classic study (chronic administration) and contemporary studies (acute administration) requires further research to correlate adequately. High colostral protein content early in piglet life is crucial for providing concentrated immunoglobulins (IgG, IgA, IgM), lactoferrin, β-lactoglobulin, α-lactalbumin, serum albumin, and low-abundance proteins (YIN et al. 2020, BRADSHAW et al. 2021). Within 24 hours postpartum, IgG and IgA levels drop significantly, while fat and lactose levels rise, highlighting the importance of early suckling for acquiring passive immunity, essential for piglet survival and growth (QUESNEL & FARMER 2019, NUNTAPAITOON et al. 2020, INOUE & TSUKAHARA 2021).

Regarding sow behavior during farrowing, our results did not show significant differences between groups. However, certain behavioral measures, such as lateral lying and dorsal arch (pre-expulsion) and lateral lying (post-expulsion), could indicate potential pain. The final hours before and during farrowing are associated with visceral pain due to dilation, distention, and contractions (NOWLAND et al. 2020). Movements such as hind leg forward-backward arching could reflect uterine contraction-related pain (ISON et al. 2018). These parameters are not extensively studied in these contexts, underscoring the need for further research on the pharmacological management of sows to improve both production and animal welfare, particularly in small-scale swine farming.

CONCLUSION

In conclusion, while our study, albeit limited in sample size, found that subcutaneous administration in the peri-vulvar area of low-dose caffeine (0.5 g/sow/predicted piglet) before farrowing did not affect farrowing duration, stillborns, or pain-related behaviours, it did lead to a significant increase in piglet weight at weaning. We also observed that longer farrowing durations correlated with decreased piglet weaning weights, whereas sows with three farrowings significantly contributed to progeny weight gain at weaning. Colostrum composition parameters showed no significant differences in fat content, but lactose levels were notably higher in the caffeine-exposed group. However, our study did not include data from smallholder pig farming, which remains significant for economic and cultural reasons. The parameters assessed are less well-documented in these systems, highlighting the need for further research to evaluate the impact of pharmacological interventions on sow management, aiming to enhance both production outcomes and animal welfare in smallholder pig farming settings.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, and formal analysis**, JASS, AYP and GVC**; investigation**, OCP, JASS and AYP**; resources and data curation**, GVC**; writing-original draft preparation**, JASS and AYP**; writing-review and editing**, JASS, AYP, TMJ and ARL**; project administration, **JASS and ARL**. All authors have read and agreed to the published version of the manuscript.

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INSTITUTIONAL REVIEW BOARD STATEMENT

The Bioethics Committee of the Academic Program in Agricultural and Livestock Development of Universidad Veracruzana approved the experimental protocol for the study (MDA-BIO-002)

INFORMED CONSENT STATEMENT

Not applicable because this study did not involve humans.

DATA AVAILABILITY STATEMENT

The data can be made available under request.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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