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Effect of maternal supplementation with creatine and caffeine prior to farrowing on piglet growth and survival: a commercial study

Final Report

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School of Animal and Veterinary Sciences, The University of Adelaide

Dr Will van Wettere

Roseworthy Campus,

South Australia, 5372

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Executive Summary

Sub-optimal pre-weaning survival significantly reduces the efficiency and profitability of the Australian, (and global) pig industry, and yet, very little improvement has occurred over the last 30 years. In excess of 700,000 live born piglets die prior to weaning (11.3%), equating to a $56 million loss of potential revenue. This project was developed based on our previous APL and SA Pig Industry funded work focussing on developing nutritional strategies to improve piglet viability at birth and thus survival. Previously, we have demonstrated increased piglet viability at birth (as evidenced by more rapid suckling post-partum), increased piglet liveweight gain (to day 3 and day 21 post-birth), and increased survival during the first three days of life (the period when over 70% of piglet mortalities occur) following maternal creatine supplementation during the last 5 days of gestation. We have also demonstrated that sows receiving oral caffeine for three days prior to farrowing had longer gestation lengths (116.6 ± 0.26 versus 115.5 ± 0.28 days; $P<0.05$) and produced 0.43 fewer still born piglets per litter. Importantly, European and Australian data clearly demonstrate that sows with short gestations (<114d) have significantly longer farrowing durations, give birth to significantly more dead piglets and wean significantly fewer piglets (Vanderhaeghe et al., 2010; van Wettere et al., unpublished). It was, therefore, hypothesised that in addition to the immediate improvements in piglet viability, caffeine supplementation may serve to reduce the incidence of short gestation lengths and, thus, lead to an improvement in the number of piglets weaned per sow. Therefore, the aim of the study was to determine whether, under commercial conditions, piglet survival and growth to weaning were increased by supplementing sow diets with caffeine (3g/day) for three days prior to parturition, or creatine monohydrate (75g/day) for five days prior to parturition, or caffeine (3g/day) plus creatine monohydrate (75g/day) for 5 days prior to parturition.

A total of 1127 sows were used in this study, with animals allocated to one of four treatment groups: Control (CONT: n=284, parity 3.5 ± 0.13); Caffeine (CAF: n=286, parity 3.4 ± 0.13); Caffeine plus Creatine (CAFCR: n=277, parity 3.1 ± 0.12); Creatine (CR: n=278, parity 3.1 ± 0.12). All sows received the same commercial sow lactation diet prior to and after farrowing, with the dietary supplements provided as a top-dress prior to farrowing. Actual durations of treatment, relative to parturition, were: 4 ± 0.11 days (range: 1 – 10 days) for CAF; 5.07 ± 0.11 days (range: 1 – 10) for CR; and 4.9 ± 0.12 days (range 1 – 12 days) for CAFCR). The optimal durations of treatment were 3 – 6 days prior to parturition for CAF, 4 days or longer prior to parturition for CR and 3 days or longer for the CAFCR. These data only, and the primary outcomes only, are discussed in this report. As parity had a significant effect on some of the measured variables, outcomes for primiparous (PP) sows were analysed separately to that of multiparous (MP) sows.

PP sows receiving CR prior to parturition lost fewer piglets prior to fostering ($P<0.05$) compared with CONT PP sows (0.39 ± 0.11 versus 0.68 ± 0.11) and had heavier litters at fostering (14.85 ± 0.32 versus 14.28 ± 0.31 kg); however, this effect was not observed in MP sows. Compared to the CONT treament group, and regardless of parity, CAF reduced ($P<0.05$) the total number of piglets per litter dying from birth to day 21 post-partum from 1.23 ± 0.08 to 0.99 ± 0.09 piglets per litter. The effect of CAF on litter weight on day 21 and weight gain to day 21 differed between PP and MP sows, with PP sows receiving CAF prior to parturition having heavier litters ($P=0.05$) on day 21 post-partum relative to CONT litters (51.90 ± 2.20 versus 48.51 ± 1.79 kg), with their litters tending to have higher weight gains ($P=0.06$) between day 0 and 21 (37.31 ± 2.12 versus 33.96 ± 1.72 kg). However, this effect was not observed in MP sows. In fact, MP sows receiving CAF had numerically lower ($P>0.1$) litter weights and litter weight gain compared with CONT sows. When compared to CONT, the impact of combining caffeine and creatine (CAFCR) on litter and piglet weight tended ($P<0.1$) to differ between parity groups, with the combined treatment appearing to increase the weight of PP sow piglets and litters but reduce the weight of MP sow piglets and litters.

It is clear from the current data that maternal parity can affect the response to pre-farrowing supplementation with either creatine or caffeine. The reason for this is unclear, but may reflect differences in uterine activity between PP and MP sows, and thus the degree of uterine trauma experienced during the parturition process. The capacity of creatine to improve piglet viability post-partum, as evidenced by reduced pre-foster mortality within PP litters, is promising. Furthermore, the capacity of caffeine to reduce mortality to day 21 of liveborn piglets regardless of maternal parity is also extremely promising. Finally, based on the current data, combining both supplements does not appear to be beneficial for piglet performance, and may in fact be detrimental. It is suggested that future work is warranted in three areas: one, to determine whether a longer period of creatine supplementation is beneficial for piglet growth and survival; two, to determine why litter weights are increased in PP but not MP sow litters when caffeine is fed pre-partum; and, three to determine with more accuracy the causes of piglet mortality in PP and MP sows, as by doing this it may be possible to tailor intervention strategies accordingly. Finally, given the relationship between piglet viability, and the reduced protection provided from sow crushing behaviours afforded in alternative (low confinement) farrowing housing, it is also proposed that creatine supplementation may be directly applicable to those systems in which sows are not confined during, or immediately after, parturition.

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1. Background to Research

Sub-optimal pre-weaning survival is a significant source of economic loss to the Australian pig industry, with the identification and evaluation of innovative solutions to improving pre-weaning survival of the piglet identified as a priority area within APL's Specialist Group 2. Based on the average pre-weaning mortality rate within the Australian sow breeding herd, 11.3% or 710,461 live born piglets died prior to weaning in 2012/ 2013 (Australian Pig Annual 2012-2013). Based on a value of $80 per piglet, this represents a loss of $56,836,880 annually. Given the economic burden associated with high incidences of pre-weaning mortality it is concerning that few improvements have been made in the past 20 years. Of even more concern is that the current push for increasing litter size will also result in an increase in neonatal mortality. Specifically, as conceptus number increases so does the duration of parturition, the variability in piglet birthweight and the number of light birthweight (<1 kg) piglets, all of which increase incidences of neonatal mortality.

This project was developed following promising outcomes when the effects of maternal supplementation with either caffeine (6g/day for three days prior to farrowing) or creatine monohydrate (75 g/day for five days prior to farrowing) on stillbirth rates, viability immediately after birth and growth to weaning were seen (van Wettere, 2016). This project was designed to determine whether, under commercial conditions, supplementing sow pre-farrowing diets with either caffeine or creatine monohydrate or both compounds together would increase piglet growth and survival to weaning. The doses used were 75 g per day of creatine monohydrate (for five days) and 6 g per day of caffeine (for 3 days), which equates to a cost of $4.13 per sow for the creatinine monohydrate supplementation or $2.75 per sow for the caffeine supplementation. With a 0.5 to 1.0 piglet reduction in pre-weaning mortality worth approximately $40 to $80, respectively (based on a piglet being worth $80), then both of these supplements represent a cost-effective and simple to implement strategy to alleviate what has been a persistent, long-lasting and costly cause of lost income to the Australian (and global) pig industry. Based on 2.2 litters per sow per year, a decrease in pre-weaning mortality of 0.5 to 1.0 piglets per litter would equate to an additional $88 to $176 per sow per year. It is also worth noting that this financial benefit doesn't include an expected increase in piglet weaning weights due to an increase in piglet viability, or at least an improvement in the vigour and viability of previously impaired piglets. The outcomes of this project meet the industry need for a cost-effective, and easy to adopt method of reducing pre-weaning mortality. A need that is driven by both economics as well as the need to address what is perceived to be a welfare concern.

2. Objectives of the Research Project

1. To determine whether a maternal dietary supplement of caffeine for three days prior to farrowing will reduce still birth rates, as well as increasing piglet viability, growth and survival.

2. To determine whether a maternal dietary supplement of creatine monohydrate for five days prior to farrowing will reduce still birth rates, and increase piglet viability, growth and survival.

3. To determine whether a maternal dietary supplement of creatine monohydrate and caffeine for five days prior to farrowing will reduce still birth rates, and increase piglet viability, growth and survival.

3. Introductory Technical Information

Intra-partum hypoxia is the primary cause of stillborn piglets and is responsible for reduced viability, survival and subsequent growth of a significant proportion of live born piglets. In addition to causing stillbirths, prolonged or intermittent oxygen deprivation during parturition results in a significant reduction in the capacity of live born piglets to adapt to extra-uterine life (evident by reduced vigour and viability; Herpin et al., 1996; Herpin et al., 2001). These low viability piglets take longer to suckle and ingest colostrum and are, therefore, more likely to die due to starvation, failure to thermo-regulate (hypothermia), reduced immune competence, or crushing by the sow. Furthermore, neonatal asphyxia has also been shown to reduce growth rate (Herpin et al., 1996), with piglets dying prior to 3 weeks having higher blood lactate levels (marker of hypoxia) at birth. It is, therefore, logical to assume that reducing the degree of asphyxia experienced by the piglets by reducing farrowing duration and / or protecting the piglet from the negative effects of asphyxia during parturition would increase piglet viability and reduce incidences of pre-weaning mortality. The use of creatine monohydrate to buffer neonates against intra-partum hypoxia is a novel, and innovative approach to a persistent and costly industry problem.

This application extends the data from my group demonstrating that supplementing sows diets with creatine monohydrate for the last five days of gestation (approximately) had a positive effect on piglet performance. Specifically, piglet viability at birth was improved (eg interval from birth to suckle was reduced and time spent suckling increased), piglet growth to day 3 and 21 post-partum was increased, as was piglet survival to day 3 post-partum (van Wettere et al., 2015 and 2017). This work was in turn based on research outcomes developed in the area of human medicine which identified that supplementation with creatine monohydrate protects the brain during hypoxic events (essentially reducing the negative effects and improving recovery; Burov et al., 2011; Shen and Goldberg, 2012), and that maternal supplementation increased creatine levels in neonatal tissue and increased capacity to cope with, and recover from, intra-partum hypoxia. More specifically, severe hypoxia results in metabolic acidemia and depletion of intracellular adenosine triphosphate (ATP), resulting in brain damage, and a reduction in post-natal growth and even death (Ireland et al., 2008). Importantly, recent studies using the spiny mouse as a model have demonstrated that increasing cellular reserves of creatine/phosphocreatine, via maternal supplementation during pregnancy, protects the foetal and neonatal brain from the consequences of oxygen deprivation (Ireland et al., 2008; Ireland et al., 2011). Spiny mice (*Acomys cahirinus*) give birth to precocial young (Ireland et al., 2008), and maternal creatine supplementation (5%) increased creatine levels in the foetal brain, heart liver and kidneys. Thought to function as a temporal energy buffer by producing ATP in the absence of oxygen, phosphocreatine essentially acts a neuro-protectant, and the neuro-protective effects of creatine supplementation in the immediate post-natal period have been demonstrated in rats and mice (Holtzman et al., 1998;

Riesberg et al., 2016). Importantly, compared to progeny from un-supplemented dams, the survival rate and post-natal growth rate of progeny from creatine supplemented dams was significantly increased following an induced hypoxic event (Ireland et al., 2008). Based on these studies, it is suggested that supplementing the diets of sows with a propensity to exhibit high stillbirth rates (e.g. higher parity sows) with creatine will reduce incidences of still births and early post-natal mortalities. Interestingly, 3 days of creatine supplementation was sufficient to protect rat pups from the negative effects of chronic, severe hypoxic insult, suggesting that including creatine in the diet for 1 week prior to farrowing (e.g. in pre-farrowing diets) may be sufficient to positively affect the neonate (Holtzman et al., 1998).

Based on the available literature in a variety of species, caffeine also has the potential to protect neonates during parturition and improve their capacity to cope with the transition to the extra-uterine environment. Caffeine is also able to cross the placental barrier (Carrilo and Benitez, 2000; Superchi et al., 2013; Dean and van Wettere, unpublished). When provided orally to sows 24 hours prior to an induced parturition, caffeine appeared to increase the viability and thermo-regulative ability of piglets (Superchi et al., 2013), and reduced the incidence of stillbirths (Superchi et al., 2016). More recent data from my group demonstrated that oral caffeine supplementation for the 3 days preceding parturition had the following positive outcomes: a 1.7 day increase in gestation length, increased piglet rectal temperature immediately post-partum, a reduction in the number of sows having stillbirths, and an overall reduction in the number of stillbirths produced. In addition to the reduced stillbirth rates, and increased rectal temperature and the capacity of caffeine to extend gestation length makes it an attractive strategy to reduce stillbirths, as sows with short gestation lengths produce more stillbirths, and lower viability piglets (Vanderhaeghe et al., 2011).

4. Research Methodology

This study was conducted in accordance with the guidelines set out in 'Code of Practice for the Care and Use of Animals for Scientific Purposes' (Canberra 2004) and with the approval of The University of Adelaide Animal Ethics Committee. All animal work was carried out at SunPork South, South Australia.

1.1 Animals, Housing and Treatments

This study used a total of 1127 Large White x Landrace Sows (PIC genetics), and was conducted over six farrowing blocks between August 2016 and May 2017. Sows were randomly allocated to one of the following four treatments at entry to the farrowing shed:

- Control (CONT): standard feeding with no supplementation (n=284 sows, parity 3.5 ± 0.13)
- Caffeine (CAF): standard feeding plus 3 g / day caffeine (n=286 sows, parity 3.4 ± 0.13)
- Creatine (CR): standard feeding plus 75 g / day creatine monohydrate (n=277 sows, parity 3.1 ± 0.12)
- Creatine plus caffeine (CAFCR): standard feeding plus 75 g / day creatine monohydrate and 3 g / day caffeine (n=278 sows, parity 3.1 ± 0.12)

Sows were housed in conventional farrowing crates through to weaning and all sows received the same diet prior to and after farrowing, with the dietary supplements provided as a top-dress prior to farrowing. Start of dietary supplement was based on predicted farrowing date, with supplementation commencing such that sows would receive a minimum of 3 days of caffeine supplementation (CAF), 5 days of creatine supplementation (CR) and 5 days of creatine plus caffeine supplementation (CAFCR). However, due to when the sows actually farrowed, the durations of treatments, relative to farrowing, were: 4 ± 0.11 days (range: 1 – 10 days) for CAF; 5.07 ± 0.11 days (range: 1 – 10) for CR; and 4.9 ± 0.12 days (range 1 – 12 for CAFCR). Piglet fostering was minimal, and occurred within treatment.

1.2 Experimental Measures

The following data were collected: gestation length, days on treatment (CAF, CAFCR and CR treatments only); total born, born alive and born dead, pre-foster and post-foster piglet mortality and post-foster litter size. In addition, litter weights were collected after fostering (Day 0) and on day 21 weights for 256, 234, 252, 243 CAF, CAFCR, CONT and CR litters, respectively.

1.3 Statistical Analysis

Data were analysed using Genstat (version 15; VSN International Ltd., Hemel Hempstead, UK). Unless otherwise specified, data are presented as Mean ± SEM, with significance accepted at P<0.05, and tendencies at P<0.1. In order to determine parity effects on all measures, as well as the impact of parity on treatment outcomes, sows were divided into two groups (primiparous (PP) versus multiparous (parity 2 and greater; MP). This parity grouping was based on analysis of the control data only, which demonstrated significantly lower stillbirths (0.65 ± 0.14 versus 1.06 ± 0.08 piglets/litter) and higher pre-foster mortality (0.76 ± 0.11 versus 0.48 ± 0.07 piglets/litter) for PP versus MP sows, respectively. The effects of treatment and sow parity on all measures were analysed using an ANOVA. Gestation length, total born and replicate were included as a co-variates when analysing treatment effects on all outcomes. Litter size suckled on day 0 (post-foster) was added to the model when analysing treatment effects on post-fostering and total piglet mortalities, as well as piglet and litter weights and weight gain.

After the initial analyses was conducted, and to make the data outcomes easier to follow, the effect of each treatment for the optimal duration of delivery was compared with the control separately. The optimal durations of treatment were 3 – 6 days prior to parturition for caffeine, 4 days or longer prior to parturition for creatine and 3 days or longer for the creatine plus caffeine treatment.

5. Results

1.1 Effect of parity groupings on piglet survival and growth (control animals only)

Total litter size was higher (P<0.05) for MP versus PP litters (13.11 ± 0.22 versus 12.18 ± 0.39). However, the number of live born piglets was similar for MP and PP sow litters (11.86 ± 0.20 and 11.38 ± 0.35 piglets), due to the higher (P<0.05) number of still born piglets in MP compared with PP sow litters (1.06 ± 0.08 versus 0.63 ± 0.15 piglets). Piglet weight and litter weight were higher (P<0.01) for MP versus PP sow litters on day 0 (1.51 ± 0.02 versus 1.23 ± 0.03 kg; 17.50 ± 0.20 versus 14.73 ± 0.6 kg) and day 21 (6.40 ± 0.07 versus 5.03 ± 0.12 kg; 63.78 ± 1.01 versus 49.72 ± 1.80 kg). Pre-foster deaths were similar (P=0.250) for MP and PP sow litters (0.51 ± 0.06 and 0.67 ± 0.11 piglets / litter), with post-foster deaths tending (P = 0.08) to be lower (0.62 ± 0.07 versus 0.89 ± 0.13 piglets / litter) and total deaths to day 21 lower (P<0.05) for MP compared with PP sow litters (1.14 ± 0.09 versus 1.56 ± 0.17 piglets / litter).

1.2 Overall treatment effects on piglet survival and growth

There was an interaction (P<0.05) between dietary treatment and sow parity for gestation length (Table 1), with both CAF and CR reducing gestation length of PP sows relative to the relevant Control, and CAF increasing gestation length in MP sows relative to the relevant Control. Total born (total

born dead and alive) was unaffected by treatment; however, compared with PP sows (P< 0.01), MP sows gave birth to more piglets in total (13.3 ± 0.11 versus 12.2 ± 0.18), but also more dead piglets (1.02 ± 0.04 versus 0.80 ± 0.07) and thus fewer live born piglets (11.7 ± 0.04 versus 12.0 ± 0.08). The number of piglets / litter dying prior to fostering was unaffected by treatment or sow parity. However, the number of piglets dying between fostering and weaning was lower (P<0.01) for MP compared with PP sows (0.60 ± 0.04 versus 1.00 ± 0.07), as was total mortality (1.16 ± 0.05 versus 1.51 ± 0.09). After fostering litter sizes were lower for MP compared with PP sows; however, litter weight after fostering, litter size on day 21 and litter weight gain to day 21 all higher for MP compared with PP sows (Table 1).

Post-fostering mortality was higher (P<0.05) for the CAFCR treatment (0.89 ± 0.07) compared with the CR (0.62 ± 0.07) and CAF (0.62 ± 0.07) treatments, with CONT (0.71 ± 0.07) similar to all treatments. There was a tendency for treatment to affect weight gain to day 21 (P=0.08). Specifically, the CR litters gaining the most weight and the CAF and CAFCR the least (Table 1).

1.3 Effect of creatine for 4 or more days prior to farrowing on piglet survival and growth

The effects on piglet survival and growth following maternal supplementation with creatine for at least 4 days prior to farrowing are presented in Table 2. There was an interaction (P<0.05) between dietary treatment and sow parity for gestation length (Table 2), with creatine increasing gestation length for MP but not PP sows. Total born was unaffected by treatment, but MP sows gave birth to more piglets in total and more dead piglets (P<0.05), and tended to give birth to more live piglets (P=0.07) compared with PP sows. MP sows also suckled larger litters on day 0 and day 21, had lower post-foster piglet mortality rates and produced heavier litters on day 21, compared with PP sows (P<0.01).

PP sows receiving creatine prior to parturition lost fewer piglets prior to fostering (P<0.05) compared with control PP sows (0.39 ± 0.11 versus 0.68 ± 0.11) and had heavier litters at fostering (14.85 ± 0.32 versus 14.28 ± 0.31 kg); however, this effect was not observed in MP sows.

1.4 Effect of caffeine for 3 to 6 days prior to farrowing on piglet survival and growth

The effects on piglet survival and growth following maternal supplementation with caffeine for 3 to 6 days prior to farrowing are presented in Table 3. Total born was unaffected by treatment, but MP sows gave birth to more piglets in total and more live and dead piglets (P<0.01), compared with PP sows. MP sows also suckled larger litters on day 0 and day 21, had lower post-foster piglet mortality rates and produced heavier litters on day 21, compared with PP sows (P<0.01).

Regardless of parity, caffeine reduced (P<0.05) the total number of piglets / litter dying from birth to day 21 post-partum from 1.23 ± 0.08 to 0.99 ± 0.09 piglets / litter. The effect of caffeine on litter weight on day 21 and weight gain to day 21 differed between the two parity groups. PP sows receiving caffeine prior to parturition had heavier litters (P=0.05) on day 21 post-partum relative to control litters (51.90 ± 2.20 versus 48.51 ± 1.79 kg), with their litters having higher weight gain (P = 0.06) between day 0 and 21 (37.31 ± 2.12 versus 33.96 ± 1.72 kg). However, this effect was not observed in MP sows. In fact MP sows receiving caffeine pre-partum had numerically lower (P>0.1) litter weights and litter weight gain compared with control MP sows.

1.5 Effect of caffeine and creatine for the 3 to 6 days prior to farrowing on piglet survival and growth

The effects on piglet survival and growth following maternal supplementation with caffeine and creatine for 3 to 6 days prior to farrowing are presented in Table 4. MP sows gave birth to more piglets in total and more live piglets (P<0.05) and tended to give birth to more dead piglets than PP sows (P=0.07). MP sows also suckled larger litters on day 0, and had lower post-foster and total piglet mortality rates than PP sow litters. MP sows also had heavier weights on day 0 and 21, and greater litter weight gain than PP sows (P<0.01).

The impact of treatment on litter and piglet weight tended (P<0.1) to differ between parity groups. CAFCR appeared to increase the weight of PP sow piglets and litters but reduced the weight of MP sow piglets and litters compared with controls (Table 4).

Table 5 Effect of Treatment (CONT (Control), CAF (Caffeine), CR (Creatine), CAFCR (caffeine plus creatine)) and Sow Parity (primiparous versus multiparous) on litter size, piglet mortality and piglet growth to weaning

Sow Parity	Primiparous					Multiparous					P values		
Treatment	CONT	CAF	CR	CAFCR	*SEM*	CONT	CAF	CR	CAFCR	*SEM*	P	Trt	P x Trt
No. Animals	71	77	78	73		213	209	199	205				
Gestation Length	116.2^{f}	115.8^{e}	115.7^{e}	115.9^{ef}	*0.09*	115.8^{e}	116.2^{f}	115.8^{e}	115.9^{ef}	*0.05*	0.51	0.12	<0.05
Litter size													
Total born	12.34^{a}	12.10^{a}	12.00^{a}	12.34^{a}	*0.18*	13.12^{b}	13.25^{b}	13.25^{b}	13.53^{b}	*0.11*	<0.01	0.87	0.6
Born alive	12.06^{b}	12.1^{b}	11.95^{b}	11.94^{b}	*0.08*	11.73^{a}	11.73^{a}	11.75^{a}	11.69^{a}	*0.04*	< 0.01	0.88	0.9
Born dead	0.72^{a}	0.71^{a}	0.90^{a}	0.88^{a}	*0.07*	1.06^{b}	0.99^{b}	0.97^{b}	1.06^{b}	*0.04*	<0.05	0.77	0.7
Piglet mortality (pigs/litter)													
Pre-foster	0.68	0.46	0.47	0.37	*0.05*	0.53	0.52	0.63	0.55	*0.03*	0.34	0.59	0.21
Post-foster	0.92^{ac}	0.97^{ac}	0.92^{ac}	1.23^{ad}	*0.04*	0.63^{bc}	0.50^{bc}	0.51^{bc}	0.77^{bd}	*0.07*	<0.01	<0.05	0.84
Total	1.60^{b}	1.44^{b}	1.40^{b}	1.60^{b}	*0.09*	1.16^{a}	1.01^{a}	1.15^{a}	1.33^{a}	*0.05*	<0.01	0.17	0.86
Litter size suckled													
Post-foster	11.96^{a}	11.94^{a}	12.10^{a}	12.11^{a}	*0.07*	11.52^{b}	11.54^{b}	11.66^{b}	11.52^{b}	*0.03*	<0.01	0.38	0.74
Day 21	9.64^{a}	9.91^{a}	9.86^{a}	9.69^{a}	*0.11*	10.07^{b}	10.05^{b}	10.21^{b}	9.84^{b}	*0.06*	<0.05	0.19	0.78
Litter weight, kg													
Day 0	14.63^{a}	14.90^{a}	15.41^{a}	15.28^{a}	*0.17*	17.45^{b}	17.39^{b}	17.26^{b}	16.91^{b}	*0.10*	<0.01	0.59	0.11
Day 21	48.49^{a}	50.04^{a}	50.54^{a}	50.09^{a}	*0.88*	63.99^{b}	61.33^{b}	63.86^{b}	60.67^{b}	*0.51*	<0.01	0.30	0.28
Litter Wt gain, kg	34.23^{a}	35.44^{a}	35.87^{a}	35.59^{a}	*0.84*	46.27^{b}	43.84^{b}	46.61^{b}	43.83^{b}	*0.49*	<0.01	0.08	0.40

Within row, different superscripts indicate significance: ^{ab}differences between parity, ^{cd}differences between treatment; ^{ef}interactive effects between treatment and parity

Table 6 Effect of creatine (CR) for four days or more prior to farrowing on piglet survival and growth compared with Control

Sow Parity	Primiparous			Multiparous			P values		
Dietary Treatment	CONT	CR D4 +	*SEM*	CONT	CR D4 +	*SEM*	P	Treat	P x Treat
No. Animals	71	64		214	157				
Gestation Length	116.2^{ef}	116.0^{ef}	*0.12*	115.8^{e}	116.3^{f}	*0.07*	0.53	<0.05	<0.05
Litter size									
Total born	12.24^{a}	12.06^{a}	*0.27*	13.14^{b}	13.04^{b}	*0.16*	<0.05	0.67	0.90
Born alive	11.44	11.18	*0.25*	11.87	11.82	*0.14*	0.07	0.67	0.71
Born dead	0.62^{a}	0.78^{a}	*0.11*	1.08^{b}	0.98^{b}	*0.63*	<0.05	0.83	0.31
Piglet mortality									
Pre-foster	0.68^{f}	0.39^{e}	*0.08*	0.52^{ef}	0.63^{f}	*0.05*	0.71	0.91	<0.05
Post-foster	0.87^{a}	0.90^{a}	*0.09*	0.60^{b}	0.54^{b}	*0.05*	<0.05	0.74	0.65
Total	1.53	1.31	*0.12*	1.13	1.17	*0.07*	0.06	0.76	0.36
Litter size suckled									
Post-foster	11.94^{a}	12.14^{a}	*0.08*	11.54^{b}	11.64^{b}	*0.05*	<0.01	0.12	0.62
Day 21	9.70^{a}	9.85^{a}	*0.15*	10.10^{b}	10.25^{b}	*0.09*	<0.01	0.30	0.99
Litter weight, kg									
Day 0	14.28^{cf}	14.85^{df}	*0.23*	17.79^{e}	17.26^{e}	*0.14*	<0.01	0.66	<0.05
Day 21	48.88^{a}	50.27^{a}	*1.27*	64.29^{b}	63.98^{b}	*0.74*	<0.01	0.64	0.55
Litter weight gain, kg	34.60^{a}	35.40^{a}	*1.20*	46.43^{b}	46.72^{b}	*0.69*	<0.01	0.53	0.85

Within row, different superscripts indicate significance: ^{ab}differences between parity, ^{cd}differences between treatment ^{ef}interactive effects between treatment and parity

Table 7 Effect of caffeine (CAF) for 3 to 6 days prior to farrowing on piglet survival and growth compared with Control

Sow Parity	Primiparous			Multiparous			P values		
Dietary Treatment	CONT	CAF	*SEM*	CONT	CAF	*SEM*	P	Treat	P x Treat
No. Animals	64	40		200	141				
Gestation length	116.2	116.0	0.12	116.0	116.3	0.06	0.67	0.11	0.08
Litter size									
Total born	12.18[a]	12.48[a]	*0.31*	13.12[b]	13.09[b]	*0.17*	<0.05	0.81	0.65
Born alive	12.02[a]	12.24[a]	*0.12*	11.68[b]	11.63[b]	*0.06*	<0.01	0.62	0.34
Born dead	0.59[a]	0.49[a]	*0.12*	1.09[b]	1.05[b]	*0.06*	<0.01	0.76	0.82
Piglet mortality									
Pre-foster	0.71	0.40	*0.09*	0.50	0.46	*0.05*	0.30	0.20	0.14
Post-foster	0.93[a]	0.71[a]	*0.10*	0.61[b]	0.49[b]	*0.05*	<0.01	0.13	0.66
Total	1.64[ac]	1.11[ad]	*0.13*	1.10[bc]	0.95[bd]	*0.07*	<0.01	<0.05	0.20
Litter size suckled									
Post-foster	12.00[a]	12.04[a]	*0.10*	11.55[b]	11.56[b]	*0.05*	<0.01	0.98	0.89
Day 21	9.56	10.03	*0.18*	9.93	10.05	*0.09*	0.21	0.88	0.13
Litter Wt, kg									
Day 0	14.28[a]	14.54[a]	*0.25*	17.71[b]	17.60[b]	*0.13*	<0.01	0.65	0.51
Day 21	48.51[e]	51.90[f]	*1.43*	64.07[g]	61.25[g]	*0.77*	<0.01	0.47	0.05
Litter Wt gain, kg	33.96[a]	37.31[a]	*1.37*	46.06[b]	43.63[b]	*0.74*	<0.01	0.54	0.06
Piglet Wt, kg									
Day 0	1.24[a]	1.25[a]	*0.02*	1.52[b]	1.51[b]	*0.01*	<0.01	1.00	0.65
Day 21	5.13[a]	5.19[a]	*0.1*	6.36[b]	6.16[b]	*0.05*	<0.01	0.24	0.22
Piglet Wt Gain, kg	3.89[a]	3.94[a]	*0.09*	4.84[b]	4.65[b]	*0.05*	<0.01	0.21	0.22

Within row, different superscripts indicate significance: [ab]differences between parity, [cd]differences between treatment; [efg]interactive effects between treatment and parity

Table 8 Effect of caffeine plus creatine (CAFCR) for 3 to 6 days prior to farrowing on piglet survival and growth compared with Control

Sow Parity	Primiparous			Multiparous			P values		
Dietary Treatment	CONT	CAFCR	*SEM*	CONT	CAFCR	*SEM*	P	Trt	P x Trt
No. Animals	71	55		214	129				
Litter size									
Total born	12.35[a]	12.03[a]	*0.28*	13.06[b]	13.78[b]	*0.17*	<0.01	0.17	0.11
Born alive	11.54[a]	11.19[a]	*0.25*	12.18[b]	12.36[b]	*0.15*	<0.05	0.28	0.13
Born dead	0.76	0.88	*0.11*	1.05	1.02	*0.06*	0.07	0.95	0.55
Piglet mortality									
Pre-foster	0.68	0.42	*0.08*	0.54	0.6	*0.05*	0.97	0.73	0.11
Post-foster	0.92[a]	1.07[a]	*0.10*	0.61[b]	0.52[b]	*0.06*	<0.01	0.85	0.28
Total	1.59[a]	1.51[a]	*0.13*	1.15[b]	1.13[b]	*0.08*	<0.01	0.79	0.85
Litter size suckled									
Post-foster	12.01[a]	12.19[a]	*0.05*	11.53[b]	11.51[b]	*0.08*	<0.01	0.52	0.32
Day 21	9.69	9.92	0.16	10.08	9.97	0.1	0.22	0.96	0.36
Litter Wt, kg									
Day 0	14.26[a]	14.81[a]	*0.24*	17.62[b]	17.19[b]	*0.14*	<0.01	0.54	0.07
Day 21	48.81[a]	51.74[a]	*1.39*	64.04[b]	61.29[b]	*0.81*	<0.01	0.38	0.07
Litter Wt gain, kg	34.48[a]	37.20[a]	*1.31*	46.39[b]	44.08[b]	*0.76*	<0.01	0.47	0.09
Piglet Wt, kg									
Day 0	1.23[a]	1.28[a]	*0.02*	1.52[b]	1.48[b]	*0.01*	<0.01	0.55	0.08
Day 21	5.09[a]	5.24[a]	*0.09*	6.36[b]	6.13[b]	*0.05*	<0.01	0.17	0.07
Piglet Wt Gain, kg	3.85[a]	3.99[a]	*0.09*	4.85[b]	4.66[b]	*0.05*	<0.01	0.23	0.10

Within row, different superscripts indicate significance: [ab]differences between parity

6. Discussion

Overall, the current data has demonstrated some subtle, yet promising, benefits for piglet survival when supplementing pre-farrow sow diets with either caffeine (3 g / day) or creatine monohydrate (75 g / day). Interestingly, creatine reduced pre-foster mortality of piglets born to primiparous sows, but did not affect mortality of multiparous sow litters. Caffeine supplementation reduced mortality rates between birth and day 21 by 0.24 of a piglet per litter, with this affect consistent across both parity groupings. Maternal caffeine supplementation also increased litter weight at day 21, as well as weight gain from day 0 to day 21 for primiparous litters; however, this effect was not observed in multiparous sow litters. In fact, caffeine appeared to reduce growth of multiparous litters.

The reduced pre-foster mortality of piglets born to creatine supplemented primiparous sows is consistent with previous evidence (Vallet et al., 2013) that creatine supplementation (1%) pre-farrowing reduced the incidences of low birth weight piglets dying as a result of layovers, particularly in primiparous sows. This reduction in overlain mortalities was attributed to increased myelination, particularly in the brain stem (Vallet et al., 2013). My previous studies in which supplementary creatine was provided to multiparous sows (n=162) prior to farrowing, demonstrated a number of positive outcomes for piglet performance. In summary, it was demonstrated that five days of maternal creatine supplementation prior to farrowing reduced the inter-piglet birth interval and time to first suckle, increased milk intake during the first 24 hours post-partum, increased piglet weight gain and survival during the first three days of life, as well survival and growth to day 21 post-partum (van Wettere, 2016). Creatine supplementation in primiparous sows also increased litter weight on day 0 of lactation, which is consistent with the increase in piglet colostrum intake and growth previously reported following maternal creatine supplementation (van Wettere, 2016). However, it remains to be established why in the current study the positive effects of creatine were only observed in primiparous and not multiparous, litters. Parturition induced hypoxia is the primary cause of intra-partum piglet deaths and, even when not fatal, can also reduce piglet viability and vitality and, as such is a primary cause of neonatal piglet mortality. Parturition, and piglet expulsion are caused by the combined effects of contractions of the smooth muscles of the uterus, and abdominal contractions powered by the skeletal muscles of the abdomen (Vallet et al., 2013). Previously we observed reduced inter-piglet birth intervals following creatine supplementation, which is consistent with the capacity of creatine to maintain ATP supplies during strenuous muscle activities (eg parturition) (Brosnan and Brosnan, 2007). Although not studied in sows, the human literature suggests that in nulliparous women, increased uterine activity is required to achieve successful birth (Arulkumaran et al., 1984). It is, therefore, plausible that the positive impact of creatine supplementation on uterine contractions may have been greater in primiparous sows, resulting in a more rapid farrowing process, and reduced risk of hypoxia. Recent evidence also suggests a regulatory effect of creatine on the immune system, which may also

explain the improved early survival of piglets born to primiparous sows, in which the immune system may be inadequate.

Based on evidence from spiny mice (Ireland et al., 2008), creatine may also improve neonatal piglet viability / vitality by protecting the neonatal brain from birth-induced hypoxia. In simple terms, during periods of oxygen deprivation, which commonly occur to varying degrees during parturition, creatine preserves mitochondrial function and acts as an energy buffer (Lawler et al., 2002; Brosnan and Brosnan, 2007; Dickinson et al., 2014). Consistent with this mechanism, maternal creatine prior to farrowing increased piglet viability and survival in our previous studies (van Wettere 2016; 2017). It might, therefore, be suggested that if uterine contractions are stronger in primiparous sows, then provision of a neuro protectant such as creatine maybe more beneficial

In contrast to creatine, caffeine reduced piglet mortalities regardless of maternal parity, with mortality rates between birth and day 21 reduced by 0.24 of a piglet per litter. Maternal caffeine supplementation for one day (Superchi et al., 2016) and three days (van Wettere, 2016) prior to parturition reduced stillbirth rates and improved piglet viability at birth. The capacity of caffeine to reduce stillbirths in the current study may be attributed to its direct beneficial effects on piglet lung function, as well as its neuro-protective capacities. In human infants, caffeine improves lung function immediately after birth, and increases lung capacity in neonates experiencing respiratory distress (Aranda et al., 2010). Improved lung function and respiration may, therefore, improve the capacity of piglets to cope with, and survive, intra-partum hypoxia and thus survive to weaning (or, in this case day 21 post-partum). Although this positive effect of caffeine was observed across both parity groupings, the benefits were, numerically at least, greater in primi- rather than multiparous sows. An outcome which may support the hypothesis that the increased uterine activity in primiparous sows increases the need for supplements which protect the fetal brain from intra-partum hypoxia and promote respiration. Alternatively, caffeine may inhibit uterine contractions, reducing the extent to which piglets are exposed to hypoxic conditions during parturition. The influence of parity on the response to caffeine is also evident in litter weights on day 21, with caffeine supplemented primiparous sows producing heavier litters on day 21 than their non-supplemented counterparts. Recently, Roldan-Santiago et al., 2017), demonstrated higher incidences of meconium staining and increased latency to teat attachment post-birth in piglets born to parity one compared with parity 2 – 6 sows. It is noteworthy that farrowing duration was unaffected by parity. These data support the current suggestion that whilst all piglets are challenged during parturition, the negative impacts on vitality, and thus potential survival, are greatest in piglets born to primiparous sows. However, whether this reflects differences in the intensity of parturition (i.e. increased contraction strength) or reduced piglet viability due to sub-optimal conditions in utero is not clear from the current data, or that of Roldan-Santiago et al. (2017).

Caffeine supplementation (6 g / day) between day 60 and 109 of gestation increased milk production and prolactin levels in primiparous sows, which could account for the increased litter weight currently observed (Li and Hacker, 1995). Alternatively, piglet stimulation of milk let down, rather than capacity to produce milk, appears to limit pre-weaning growth in piglets suckling primiparous sows, with the capacity to produce milk the limiting factor for piglets suckling multiparous sows. Consequently, an improvement in piglet viability and vitality, and hence suckling activity could account for the increased litter weight observed in caffeine supplemented primiparous but not multiparous litters. Previous work in my group (unpublished), has demonstrated increased suckling behaviour in piglets immediately after receipt of oral caffeine, with our own, and previous work, demonstrating improvements in piglet thermoregulation and vigour at birth following maternal caffeine supplementation pre-parturition (Superchi et al., 2013; van Wettere, 2016). However, it is worth noting that caffeine resulted in numerical, but not significant, increases in both piglet weight and litter size on day 21, which may have been responsible for this increase in litter weight. Although not significant, caffeine appeared to reduce piglet and litter weight at day 21 in multiparous sows, supporting the notion that caffeine's effects differ between maternal parity groupings.

Caffeine supplementation also increased gestation length in multiparous sows, which is consistent with our previous study in which multiparous sows received 6 g of caffeine daily for approximately three days prior to parturition (van Wettere, 2016). In the current study, parturition occurred on average 0.4 of a day later in caffeine supplemented sows, whereas the daily supplementation of 6 g caffeine extended gestation length by 1.3 days. From a commercial perspective, extensions in gestation length (or prevention of premature farrowings) may be beneficial. Sows which farrow early (< d 114 post-insemination) give birth to more dead piglets, with their live born piglets more likely to die prior to weaning, presumably due to reduced piglet maturity at the onset of parturition and longer farrowing durations (Zaleski and Hacker, 1993; van Dijk et al., 2005; Vanderhaughe et al., 2011)

The combination of the two supplements resulted in no changes in piglet survival or growth. However, without determining whether the effects of creatine and caffeine are mediated via direct improvement in piglet viability or indirectly via alterations in uterine contractions, an explanation for this outcome cannot be made. However, based on the assumption that creatine promotes and caffeine inhibits uterine contractions, it could be hypthesised that the two compounds are essentially cancelling each other out.

In addition to the effects of the supplements on piglet survival and growth, a profound effect of maternal parity was also observed. Litter growth and weight on day 21 were both higher for

multiparous compared with primiparous sows, presumably reflecting increased milk production as well as reduced mortality of live born piglets. However, what is particularly concerning from a productivity perspective is that despite giving birth to almost an extra piglet per litter, the increased incidence of stillborn piglets means that only marginally more live born piglets are produced by higher parity sows. The reproductive potential of this population of sows does, therefore appear to be limited by high incidences of stillbirths. Increased stillbirths can be attributable primarily to increased duration of parturition, suggesting that future work is required to improve management of multiparous sows prior to, and during, parturition, such that farrowing duration is decreased and stillbirth rates are decreased. In contrast, total piglet mortality was higher in primiparous compared with multiparous sows, which may reflect differences in piglet potential (due to sub-optimal intra-uterine environment), reduced piglet viability at birth (due to increased uterine activity immediately pre-birth) or reduced colostrum and / or milk production. It is, therefore, suggested that future work focusses on establishing the precise causes (or causes) of this reduced performance to weaning, with subsequent work developing alleviation strategies.

In summary, it is clear from the current data that maternal parity can affect the response to pre-farrowing supplementation with either creatine or caffeine. The reason for this is unclear, but may reflect differences in uterine activity between primi- and multiparous sows, and thus the degree of uterine trauma experienced during the parturition process. The capacity of creatine to improve piglet viability post-partum, as evidenced by reduced pre-foster mortality within primiparous litters, is promising. Furthermore, the capacity of caffeine to reduce mortality to day 21 of liveborn piglets regardless of maternal parity is also extremely promising. Finally, based on the current data, combining both supplements does not appear to be beneficial for piglet performance, and may in fact be detrimental. Based on these data, it is suggested that future work is warranted in three areas: one, to determine whether a longer period of creatine supplementation is beneficial for piglet growth and survival; two, to determine why litter weights are increased in primiparous but not multiparous litters when the sows received caffeine pre-partum; and, three to determine with more accuracy the causes of piglet mortality in primiparous and multiparous sows, as by doing this it may be possible to tailor intervention strategies accordingly. Finally, given the relationship between piglet viability, and the reduced protection provided from sow crushing behaviours afforded in alternative (low confinement) farrowing housing, it is also proposed that creatine supplementation may be directly applicable to those systems in which sows are not confined during, or immediately after, parturition.

7. Implications & Recommendations

When analysed separately, it is clear the different treatments had some positive effects on litter performance, interestingly, many of these effects were parity dependant. Specifically,

- Creatine decreased pre-foster mortality in primiparous litters resulting in an increased suckled litter size 24 hours post-birth

- Caffeine decreased total mortality between birth and day 21, and increased weight of primiparous litters on day 21

- The combination of creatine and caffeine did not affect piglet mortality, but appeared to increase weight of primiparous litters and decrease weight of multiparous litters.

Based on these data, it is suggested that future work is warranted in four areas:

1. To determine whether a longer period of creatine supplementation is beneficial for piglet growth and survival.

2. To determine why litter weights are increased in primiparous but not multiparous litters when the sows received caffeine pre-partum.

3. To determine with more accuracy the causes of piglet mortality in primiparous and multiparous sows, as by doing this it may be possible to tailor intervention strategies accordingly.

4. To determine why the vitality of piglets born to primiparous sows is lower (does it reflect differences in parturition process or sub-optimal conditions *in utero*), and should strategies to improve piglet viability be focussed towards this group of animals.

Also, given the relationship between piglet viability, and the reduced protection provided from sow crushing behaviours afforded in alternative (low confinement) farrowing housing, it is also proposed that creatine supplementation may be directly applicable to those systems in which sows are not confined during, or immediately after, parturition.

8. Technical Summary

Caffeine or Creatine can improve piglet survival and performance

To determine whether adding creatine (75 g / day) or caffeine (3 g / day) individually or together to sow diets prior to farrowing would reduce piglet mortalities and increase piglet growth to weaning. Creatine consumption was targeted for the 5 days prior to farrowing and Caffeine for 3 days prior to farrowing.

- Neither supplement affected stillbirth rates
- There were no beneficial effects of combining the two supplements
- 3 – 6 days of caffeine supplementation prior to farrowing decreased piglet mortality to day 21 post-partum
- 3 – 6 days of caffeine supplementation of primiparous sow diets increased litter growth to day 21 and litter weight on day 21
- 4 or more days of creatine supplementation prior to farrowing reduced the mortality of primiparous piglets during the first 24 hours of life.
- Stillbirth rates are higher for multiparous sows; however, post-foster deaths are higher in primiparous sows.
- The viability and vigour of piglets which survive parturition may be lower in primiparous compared with multiparous litters.
- Future research should focus on determining why the vitality of piglets born to primiparous sows is lower (does it reflect differences in parturition process or sub-optimal conditions *in utero*)

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