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van Wettere, WHEJ, Toplis, P and Miller, HM orcid.org/0000-0003-1440-0454 (2018) Effect of oral progesterone and caffeine at the end of gestation on farrowing duration and piglet growth and survival. animal, 12 (8). pp. 1638-1641. ISSN 1751-7311

https://doi.org/10.1017/s175173111700310x

Effect of oral progesterone and caffeine at the end of gestation on farrowing duration and piglet growth and survival

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Short Title: Regumate, Caffeine and piglet survival

ABSTRACT

The profitability of pig production is constrained by high incidences of peri-parturient and pre-weaning piglet mortality. Supplementing sows with either progesterone or caffeine during the last week of gestation can reduce stillbirths and improve piglet performance. However, the consequences of combining these two substances has not been investigated. The aim of the current study was to determine the effect of oral supplementation of sows with regumate and caffeine at the end of gestation on the timing and progression of farrowing, as well as piglet survival and growth to weaning. From day 111 to 113 of gestation, 20 Large White pregnant sows (parity 3.0 ± 0.45) received 5 ml of Regumate Porcine (0.4 w v oral solution; MSD Animal Health) daily on top of their morning ration. Sows were stratified according to parity and predicted farrowing date, and allocated at random to receive a diet supplemented with either 0 g caffeine / kg diet (CONT) or 2.4 g of caffeine / kg diet (CAFF) from day 113 of gestation until parturition (n = 10 sows / treatment). Treatment did not affect total litter size; however, CONT sows gave birth to more live and fewer dead piglets compared with CAFF sows; 14.5 ± 0.73 versus 11.7 ± 1.03 and 0.7 ± 0.20 versus 3.2 ± 0.77; $P < 0.05$). Mean, minimum and maximum piglet birthweight were unaffected by treatment. Treatment (CONT versus CAFF) reduced the proportion of piglets with a birthweight < 1 kg (0.05 ± 0.02 versus 0.16 ± 0.05; $P = 0.072$) and increased the proportion of live born piglets surviving to day five post-partum (0.90 ± 0.02 versus 0.77 ± 0.06; $P < 0.05$) and to weaning (0.90 ± 0.02 versus 0.74 ± 0.06; $P < 0.05$) Overall, the current data provided the first evidence that caffeine supplementation of sows receiving progesterone to prevent premature farrowing impaired piglet survival during, and shortly after parturition. This negative outcome may be linked to extended farrowing durations, an inhibitory effect of progesterone on maternal caffeine metabolism or an

increase in the proportion of very light piglets at birth. These data provide compelling, albeit preliminary, evidence that caffeine and progesterone should not be used together at the end of gestation.

Key words: Caffeine, progesterone, stillbirths, piglet, sow

Implications

High rates of still born piglets and early post-natal piglet deaths continue to limit productivity of pig production. Previously, maternal caffeine supplementation prior to farrowing reduced stillbirth rates, and oral progesterone (regumate) at the end of gestation preventing early farrowing and, thus, reduced stillbirths. However, the current data demonstrated that supplementary caffeine in conjunction with regumate at the end of gestation increased piglet mortality during, and after, farrowing. It is concluded that these two compounds should not be used together.

Introduction

High incidences of piglet mortality, either during parturition or prior to weaning, continue to limit the efficiency and profitability of pig production. Intra-partum hypoxia is the primary cause of still born piglets, and is responsible for reduced viability, survival and subsequent growth of a significant portion of live-born piglets (Herpin et al., 1996; Herpin et al., 2002). It is, therefore, logical to assume that protecting the piglet from the negative effects of oxygen deprivation during parturition will increase piglet viability and reduce incidences of pre-weaning mortality. One compound with neuroprotective properties, as well as the capacity to stimulate respiration in newborns, is caffeine. In sows, maternal caffeine supplementation on the day prior to an induced parturition

(Superchi et al., 2016), or for three to four days prior to natural farrowing (Dearlove et al., 2015) significantly reduced incidences of stillbirths. Maternal caffeine supplementation also improved piglet thermoregulation (Superchi et al., 2013; Dearlove et al., 2015), and increased gestation length by 1.1 days (Dearlove et al., 2015).

The capacity of maternal caffeine supplementation to delay the onset of parturition is of particular interest. Short gestation lengths are associated with increased stillbirths and pre-weaning mortality (Vanderhaughe et al., 2011), reflecting reduced piglet maturity at onset of parturition (Zaleski and Hacker, 1993) and longer farrowing durations (van Dijk et al., 2005). Subsequently, both Vanderhaughe et al. (2011) and Gaggini et al. (2013) demonstrated that oral progesterone at the end of gestation is an effective and safe strategy to prevent early farrowing. However, newborn piglets may still have reduced vitality at birth following maternal progesterone treatment prior to farrowing and therefore we hypothesised that the addition of caffeine at the end of gestation would improve newborn piglet vitality and reduce neonatal mortality. The effect of combining caffeine and regumate on gestation length and farrowing outcomes has not been reported in the literature. The aim of the current study was, therefore, to determine the effect of oral supplementation of sows with regumate and caffeine at the end of gestation on gestation length, farrowing duration, stillbirth rates and pre-weaning growth and survival of live born pigs.

Materials and methods

Animals

This experiment was conducted at the University of Leed's Research Piggery during autumn 2016 (October / November). Twenty Large White pregnant sows (parity 3.0 ± 0.45 (Mean ± SEM); range 1 - 8) were moved to farrowing crates 7.1 ± 0.34 days (range 6 – 11 days) prior to predicted farrowing date (gestation day 115). From day 111 to 113 of gestation, all sows received 5 ml of Regumate Porcine (0.4 w v oral solution; MSD Animal Health) daily on top of their morning ration. Sows were stratified according to parity and predicted farrowing date, and allocated at random to receive a diet supplemented with either 0 g caffeine / kg diet (CONT) or 2.4 g of caffeine / kg diet (CAFF) from day 113 of gestation until parturition (n = 10 sows / treatment). As per routine husbandry at the Leeds piggery, sows were fed 2.0 kg / day of gestation diets (12.5 MJ kg/DE; 11.64% protein; 4% fibre; 0.45% total lysine) from farrowing crate entry until day 3 post-farrowing.

Experimental measures

The total number of piglets born, born alive and dead, and the number of mummified foetuses produced were recorded for all sows. Using installed video cameras, the following measures were also collected; duration of farrowing and inter-piglet birth intervals. The start of parturition was defined as the expulsion of the first piglet, and the end of parturition defined as the time at which placental tissue was expelled. Piglets born alive and dead were weighed on the day of birth (birthweight; BW). Piglets were weighed individually on day 5.2 ± 0.39 post-partum and at weaning (25.2 ± 0.39 days post-partum). Piglet mortality was recorded throughout lactation. Cross-fostering only

occurred after birthweights had been taken and piglets identified, and was kept to a minimum.

Statistical analyses

Data is expressed as Mean ± SEM (unless otherwise stated). All data were analyzed as a randomized complete block design, with individual sow as the experimental unit. The effect of pre-farrowing dietary treatment on all measures was determined using a one-way ANOVA (Genstat version 15; VSN International Ltd., Hemel Hempstead, UK), with sow parity included as a co-variate. Total litter size was also added to the model, as a co-variate, when determining treatment effects on piglet weight, growth, farrowing duration and inter-piglet birth interval. A chi-squared analysis was used to determine treatment effects on the distribution of piglets within four BW categories (< 1.0 kg, 1.01 – 1.2 kg, 1.21 – 1.6 kg, > 1.6 kg), as well as the survival of the piglets within BW category. Treatment means were statistically separated using the LSD option, with $P \leq 0.05$ indicating a difference and $P \leq 0.10$ indicative of a trend/tendency.

Results

The total number of piglets born was unaffected by treatment. The number of still born piglets was lower ($P < 0.05$) and the number of live born piglets higher ($P = 0.054$) for CONT compared with CAFF sows (Table 1). Piglet survival to day five post-partum (% total born and % live born piglets) was higher ($P < 0.05$) for the CONT compared with CAFF treatment (Table 1). There were no treatment effects (CONT versus CAFF) on piglet BW: mean (1.52 ± 0.07 and 1.37 ± 0.06 kg; $P = 0.124$); minimum (1.03 ± 0.10 and 0.80 ± 0.09 kg; $P = 0.107$) or maximum (1.89 ± 0.08 and 1.80 ± 0.10 kg; $P = 0.399$). CONT litters contained a lower proportion of piglets with a BW < 1 kg (0.05 ± 0.02

versus 0.16 ± 0.05; P = 0.072). There was a tendency for CONT piglets to be heavier on day five post-partum (P = 0.063) and at weaning (P = 0.098) (2.17 ± 0.11 versus 1.96 ± 0.13 kg and 6.98 ± 0.31 versus 6.01 ± 0.56 kg, respectively). However, piglet growth rate from birth to weaning was similar (P = 0.118) for CONT and CAFF litters (0.218 ± 0.01 and 0.183 ± 0.02 kg / day). CONT sows weaned more piglets than CAFF sows (12.9 ± 0.53 versus 8.7 ± 0.96, and piglet survival to weaning (% total born and % live born piglets) was higher (P < 0.05) for the CONT compared with CAFF treatment (Table 1).

Overall, the proportion of < 1.0 kg BW piglets was lower in the CONT compared with CAFF treatments (0.06 versus 0.16). Treatment (CONT versus CAFF) increased the proportion of < 1.0 kg BW piglets alive at birth (0.88 versus 0.51; P < 0.1) but not at weaning (Table 2). The proportion of 1.21 – 1.60 kg BW piglets alive at birth and at weaning was higher for the CONT versus CAFF treatments (Table 2). Farrowing duration and inter-piglet birth interval were similar for the CONT and CAFF treatment groups (Table 1).

Discussion

The current data demonstrated that oral caffeine supplementation at the end of gestation increased piglet mortality, both during and soon after parturition, when provided to sows receiving progesterone to prevent premature farrowing. This finding contradicts previous studies in which the effects of caffeine supplementation or progesterone supplementation at the end of gestation were investigated separately. Previous data indicated lower still births, and improved piglet thermoregulation,

following maternal supplementation with caffeine for one (Superchi et al., 2016) and three (Dearlove et al., 2015) days prior to farrowing. Using the same protocol as the current study, oral progesterone prevented premature farrowings and the associated impairment of piglet survival and growth (Vanderhaughe et al., 2011; Gaggini et al., 2013).

The mechanisms responsible for the negative effect of caffeine, concurrent with and after, progesterone supplementation, on peri-parturient piglet survival cannot be established from the current data. Previous reports of lower stillbirth rates following maternal caffeine supplementation (Dearlove et al., 2015; Superchi et al., 2016), have been attributed to increased uterine contractility, and therefore a more rapid birth process (Superchi et al., 2016). However, the potent inhibitory effects of caffeine on myometrial contractility have been demonstrated consistently in uterine tissue of pregnant rats (Martin et al., 1989; Savineua et al., 1990; Apaydin et al., 1998; Martin et al., 1999). Support for the notion that the currently observed increase in still births reflected an inhibitory effect of caffeine on uterine contractility was provided by the numerical, albeit non-significant, increase in both total farrowing duration and inter-piglet birth intervals. Previous studies report no impact of caffeine on farrowing duration (Dearlove et al., 2015; Superchi et al., 2016) or inter-piglet birth interval (Dearlove et al., 2015), suggesting an interactive effect between progesterone and caffeine was responsible for the apparent extension of parturition in the current study. Kirkwood et al. (1985) concluded that oral progesterone supplementation prevents parturition by inhibiting myometrial contractions. It is, therefore, plausible that supplementation with two inhibitors of uterine contractility in close succession was responsible for the current extension of parturition and increase in piglet mortality.

Caffeine supplementation increased the proportion of piglets in the litter with very low (< 1 kg) birthweights, which contradicts previous evidence that three days of caffeine supplementation (6 g / day) prior to farrowing did not alter birthweight (Dearlove et al., 2015). However, one day of caffeine supplementation (approximately 6.4 g per sow) on the day of farrowing induction tended to reduce piglet weight at birth and day five post-partum (Superchi et al., 2013), and high caffeine intakes in pregnancy are associated with reduced fetal growth and low birthweights in humans (Hoyt et al., 2014; Partosch et al., 2015). Caffeine crosses the human placenta (Partosch et al., 2015), and maternal caffeine supplementation increased plasma levels in newborn piglets (van Wettere and Dean, unpublished). In humans, caffeine cannot be metabolized by the placenta or fetus (Grosso et al., 2006), and prolonged periods of maternal caffeine intake expose the fetus to increasing levels of caffeine (Partosch et al., 2015). Oral contraceptive pills inhibit caffeine metabolism, potentially explaining the reduced caffeine metabolism observed during the third trimester in women (Balogh et al., 2005; Partosch et al., 2015). It is, therefore, suggested that the increased incidence of low birthweight piglets observed in the current study reflects alterations in fetal growth in response to caffeine. Furthermore, it is possible that orally dosing sows with progesterone in the current study further inhibited maternal caffeine metabolism and clearance. As a result, fetuses were exposed to higher levels of caffeine than in previous studies (Dearlove et al., 2015), potentially explaining the increased incidence of low birthweight piglets and contributing to increased preweaning mortality.

In conclusion, regardless of the mechanisms responsible, the current data provides what is, to the best of our knowledge, the first evidence that using progesterone in

combination with caffeine at the end of gestation has negative outcomes for the piglet. This is an important finding for two reasons; one, it will prevent producers from combining these two substances; and two, it demonstrates the importance of understanding how caffeine affects neonatal piglet growth, the progression of parturition and piglet viability before recommendations are made for its commercial use.

Acknowledgements

The authors would like to acknowledge Primary Diets for kindly providing the diets which were used in this study.

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296 Table 1 Effect of maternal diet (control (CONT) versus caffeine (CAFF)) on litter
297 characteristics, farrowing duration, interpiglet birth interval and piglet survival

	Treatment		Pooled	P value
	Control	Caffeine	SEM	
Litter size				
Total born	15.3	14.9	0.88	0.770
Born alive	14.5	11.7	0.85	0.032
Stillborn	0.7	3.2	0.58	0.006
Mummified	0.11	0.00	0.07	0.278
Farrowing duration, mins	304.7	478.8	91.7	0.394
Inter-piglet birth interval, mins	21.5	33.4	5.6	0.362
Piglet survival, day 5 post-partum				
Prop. Total born	0.86	0.60	0.04	<0.001
Proportion born alive	0.90	0.77	0.04	0.037
Piglet survival, weaning				
Prop. Total born	0.86	0.58	0.05	<0.001
Proportion born alive	0.90	0.74	0.04	0.007

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Table 2 Effect of piglet birth weight category and maternal diet (caffeine (CAFF) versus control (CONT) on the proportion of piglets born alive and the proportion of piglets alive at weaning.

	Piglet Birthweight Category			
	< 1 kg	1.01 - 1.2 kg	1.21 - 1.6 kg	> 1.6 kg
Prop. born alive				
CONT	0.88*^{c}	0.89^{c}	1.00^{bd}	0.98^{cd}
CAFF	0.51*^{c}	0.85^{d}	0.77^{ad}	0.97^{d}
Prop. alive at weaning				
CONT	0.22^{c}	0.78^{cd}	0.96^{bd}	0.90^{d}
CAFF	0.13^{c}	0.62^{d}	0.62^{ad}	0.82^{d}

Within column, and time period superscripts indicate differences between CAFF and CONT; ^{ab} $P < 0.05$; * $P < 0.1$,
Within row, different superscripts indicate differences; $^{cd}P < 0.05$