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Effect of tolfenamic acid in postpartum gilts and the performance of their piglets

Efeito do ácido tolfenâmico no pós-parto de leitoas e no desempenho da leitegada

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Highlights

Tolfenamic acid administration decreases piglet mortality until 18 days of age.
Tolfenamic acid administration promotes weight gain in piglets.
Tolfenamic acid administration does not affect postpartum dysgalactia syndrome.

Abstract

Postpartum dysgalactia syndrome (PPDS) is a common disorder affecting sows in intensive production systems. In most cases, hypogalactia is not clearly identified and assumes a subclinical aspect. Therefore, the present study aimed to evaluate the effect of a nonsteroidal anti-inflammatory drug (NSAID) based on tolfenamic acid as a prophylactic treatment for PPDS and the performance of suckling piglets. Gilts (n = 319) were randomly divided into two groups: a tolfenamic acid group (n = 157) and a control (n = 162). The tolfenamic acid group received a single intramuscular injection (1 ml/20 kg of 4% tolfenamic acid) after farrowing, whereas the control group received no treatment. The occurrence of PPDS was confirmed. All piglets (n = 4,466) were weighed at 1, 4, and 18 days of age. All litters were evaluated for weight gain, the occurrence of diarrhea, and mortality between 4 and 18 days of age. PPDS variables were analyzed using logistic regression. Piglet weights were analyzed based on covariance while considering the effects of initial weight and the presence of diarrhea. Tolfenamic acid had no significant effect on the incidence of PPDS. The tolfenamic acid group had a 0.41% lower piglet mortality rate until 18 days of age. Tolfenamic acid administered prophylactically to gilts after farrowing reduced piglet mortality during lactation and promoted weight gain.

Key words: Litter mortality. Non-steroidal anti-inflammatory drug. Postpartum dysgalactia syndrome. Suckling piglets.

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Resumo

A síndrome da disgalactia pós-parto (PPDS) é uma doença comum e importante que afeta as matrizes suínas em sistemas intensivos de produção. Na maioria dos casos, a hipogalactia não é claramente identificada, assumindo um aspecto subclínico. Portanto, o presente estudo teve como objetivo avaliar o efeito de um medicamento anti-inflamatório não esteroide (AINE) baseado em ácido tolfenâmico como tratamento profiláctico para PPDS e o desempenho de leitões em aleitamento. As leitoas (n = 319) foram divididas aleatoriamente em dois grupos de tratamento: um grupo de ácido tolfenâmico (n = 157) e um grupo de controle (n = 162). O grupo tratado recebeu uma única injeção intramuscular (1 ml/20 kg de 4% de ácido tolfenâmico) após o parto, enquanto que o grupo de controle não recebeu nenhum tratamento. A ocorrência de PPDS foi então verificada. Todos os leitões (n = 4466) foram pesados com 1, 4, e 18 dias de idade. Todas as leitegadas foram avaliadas quanto ao ganho de peso, ocorrência de diarreia e mortalidade entre os 4 e 18 dias de idade. As variáveis PPDS foram analisadas através de regressão logística. Os pesos de leitões foram analisados com base na covariância, considerando os efeitos do peso inicial e a presença de diarreia. Não houve efeito significativo do ácido tolfenâmico sobre a ocorrência de PPDS. O grupo do ácido tolfenâmico teve menos 0,41% de mortalidade dos leitões até aos 18 dias de idade. O ácido tolfenâmico administrado profilaticamente nas leitoas após o parto reduziu a mortalidade dos leitões durante a lactação e aumentou o ganho de peso nos leitões.

Palavras-chave: Mortalidade dos leitões. Medicamento anti-inflamatório não esteroide. Síndrome de disgalactia pós-parto. Leitões em aleitamento.

Introduction

The immunocompetence of sows can be impaired by birth condition challenges that leave them more vulnerable to diseases during the initial lactation period (Friendship & O'Sullivan, 2015), especially postpartum dysgalactia syndrome (PPDS).

PPDS is a pathological condition that can occur in sows and gilts during the postpartum period and is characterized by insufficient colostrum and milk production, which triggers starvation and increased mortality in piglets and may also cause infections in the uterine tracts and udders of sows (Farmer et al., 2019). Owing to its complex physiopathology and multifactorial nature, PPDS affects sows in puerperium, especially primiparous individuals (Tummaruk et al., 2010; Ison et al., 2018). Moreover, PPDS is one of the main causes of neonatal problems in piglets and financial losses in pig farming (Niemi et al., 2017).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended for the treatment of sows to relieve pain and discomfort. According to Johnson et al. (2019), NSAIDs are effective and financially viable drugs that are easy to administer. The NSAIDs recommended for this purpose include flunixin, meloxicam, ketoprofen, and tolfenamic acid.

Previous studies have addressed the effects of the administration of NSAIDs, particularly, meloxicam (Mainau et al., 2012, 2016), flunixin (Tummaruk & Sang-Gassanee, 2013) and ketoprofen (Claeyé et al., 2015; Homedes et al., 2014; Viitasaari et al., 2013), on the treatment of PPDS (Hirsch et al., 2003; Tummaruk & Sang-Gassanee, 2013) and litter development.

Although some studies have shown positive effects related to the use of NSAIDs during the postpartum period, the use of these compounds has yielded variable results, suggesting the need for further studies because these compounds differ in anti-inflammatory, analgesic, and antipyretic properties (Ison et al., 2017; Karriker et al., 2019; Mainau et al., 2016; Schoos et al., 2019).

Considering the importance of PPDS in the performance and welfare of sows, the objective of this study was to evaluate the effects of NSAID based on tolfenamic acid administered during the postpartum period as a prophylactic treatment for PPDS on the mortality and litter performance of gilts.

Material and Methods

Animals, housing, and experimental design

The use of animals and all experimental procedures were approved by the Ethics Committee on the Use of Animals of EMBRAPA Swine and Poultry (protocol number: nº27/2018).

This study was performed between February and May 2019 in a piglet production unit with a capacity of 2,000 sows located in the southern region of Brazil, which has a predominantly subtropical climate.

A total of 319 gilts belonging to two commercial breeds (A and B; both ½ Landrace × Large White ½) and their respective litters were evaluated. The gilts were housed under identical conditions during pregnancy (in individual cells with solid floors, automatic feeders, and manual curtains). The maternity facility had individual farrowing crates with creep areas and steel guard rails to prevent overlays. Farrowing crates were 2.40 × 2.80 m with metal slatted floors for sows and plastic slatted floors for piglets.

Gilt insemination occurred between 189 and 285 days of age. In the third trimester of pregnancy, gilts were fed once per day with 1,900 g of gestation diet based on corn, soybean meal, and vitamin premix at the following nutritional levels:12.4% crude protein, 0.6% digestible lysine, and 3,230 kcal of metabolizable energy per kg of feed. From the lactation period until weaning, the gilts received ad libitum lactation rations with the following nutritional levels:18.5% crude protein and 3,360 Kcal of metabolizable energy per kg of feed. Water was provided *ad libitum* throughout the study.

The gilts were randomly divided into two groups on the day of farrowing (day 0), with 157 gilts in the treatment group and 162 in the control group. The gilts belonged to two commercial breeds, namely, Agroceres PIC® (A) (n = 254; 130 control group and 124 treatment group) and DANBRED® (B) (n = 65; 32 control group and 33 treatment group). After parturition, each gilt in the experimental group was injected intramuscularly in the neck region with 10 mL of Tolfedine CS® [8 mg/kg of body weight (BW) tolfenamic acid]. The product was applied within 15 hours of the birth of the last piglet.

Each gilt was identified and the following items were recorded: date of farrowing, age at the time of insemination, date of insemination, the total number of viable ceilings, breed, body condition score at accommodation and weaning, date of loading into the farrowing room, expected farrowing date, room number, and farrowing

cage. Throughout the study period, the temperature and humidity in the experimental facilities were recorded using data loggers.

Measurements

Gilts and their litters were evaluated daily by measuring the rectal temperature from the 1st to the 3rd day after uniformity. The presence and classification of vulvar discharge (absent/present) and its appearance (normal, abnormal, or mucopurulent) were assessed. Gilts that presented rectal temperatures over 39.5 °C were considered to have hyperthermia, while those with rectal temperatures over 39.8 °C were considered to be in a feverish state. Gilts that presented mucopurulent vulval discharge, rectal temperatures above 40 °C, and/or anorexia were medicated with a single dose of marbofloxacin (Forcyl®).

During farrowing, the number of total-born, live-born, stillborn, and mummified piglets was recorded. Piglets that were born alive were individually weighed at birth and at 4 and 18 days of age. Gilts that presented body temperatures above 39.5 °C from the 1st to the 3rd day after delivery with vulval discharge were considered to have PPDS.

The piglets were evaluated individually and daily for diarrhea over an 18-day period. The number of piglets with diarrhea in each litter and the number of live piglets were recorded. Litters in which more than 30% of piglets had diarrhea in the same evaluation were considered litters with diarrhea. The number of dead piglets and the causes of mortality were recorded. No live piglets were removed during the 18 days of evaluation.

Statistical analysis

All statistical analyses were performed using Statistical Analysis System (SAS) (SAS 9.1, SAS Institute Inc., Cary, NC, USA). Gilts and litter were considered the experimental units. Normality tests of the data and residuals were performed for all evaluated variables. The significance level was set at $p < 0.05$.

The occurrence of PPDS in gilts and diarrhea in litters were analyzed using Poisson distribution. Descriptive data (total piglets born, live-born piglets, piglets alive at 4 days of age, piglets alive at 18 days of age, pregnancy duration, the interval between housing and farrowing, number of functional ceilings, and number of total ceilings) were assessed via deviance analysis including the effects of treatment, female breed, and the interaction of both. For these characteristics, a Poisson distribution was considered and the GENMOD procedure was applied in SAS.

Piglets with diarrhea at 1 to 18 days of age were analyzed using Generalized Estimating Equations (GEE) (SAS GENMOD package). The litter performance variables (average weight at 4 days of age, average weight at 18 days of age, total litter weight at 4 days of age, total litter weight at 18 days of age, and total litter weight gain at 18 days of age) were analyzed using covariance analysis, considering the effects of treatments and the incidence of diarrhea in the litter using the GLM procedure.

For piglet mortality data at 4 and 18 days of age, as well as total mortality, logistic regression was performed by considering the effects of the treatments, the presence of diarrhea in the litter, and the initial average weight of the litter. The overdispersion of these response variables was corrected using Pearson's chi-squared test.

Results and Discussion

Descriptive analysis of gilts and their respective litters was similar between the groups (p>0.05) (Table 1). The frequency of gilts with PPDS did not differ between the treatments (Table 2).

Table 1
Descriptive variables (mean ± SE) for gilts and litters according to treatment (control vs. tolfenamic acid)

Parameters	Control (n = 162)	Tolfenamic acid (n = 157)	Pr>F
Gilts			
Gestation length (days)	115.06 ± 0.10	114.99 ± 0.09	0.9269
Farrowing length (min)	313.43 ± 7.51	303.01 ± 7.09	0.4200
Nº of function ceilings	14.95 ± 0.07	14.96 ± 0.06	0.8037
Nº of ceilings	15.40 ± 0.08	15.50 ± 0.07	0.7853
Farrowing interval (days)	2.95 ± 0.128	2.930 ± 0.11	0.3973
Litter			
Total born	15.55 ± 0.23	15.55 ± 0.21	0.9946
Total born alive	14.51 ± 0.21	14.54 ± 0.19	0.9110
Total stillborn	0.65 ± 0.080	0.68 ± 0.072	0.6036
Initial weight per piglet (g)	1316.1 ± 14.7	1306.1 ± 13.5	0.7909
Initial weight per litter (kg)	18.43 ± 0.15	18.29 ± 0.13	0.7054

SE= Standard error.

Table 2
Reproductive performance and the occurrence of postpartum dysgalactia syndrome (mean ± SE) according to treatment (control vs. tolfenamic acid)

Parameters*	Control	Tolfenamic	Pr>χ^2
Number of piglets at day 4	13.36±0.08	13.36±0.07	0.9756
Number of piglets at day 18	13.00±0.10	13.06±0.08	0.9579
Number of piglets >3kg at day 18	12.45±0.12	12.34±0.12	0.9734
Discharge vaginal (%)	16.67±2.94	20.38±3.23	0.3774
Body temperature >39.5°C (%)	40.12±3.86	43.31±3.97	0.5378
PPDS1 (%)	51.85±3.94	54.14±3.99	0.6449

[1]Gilts presenting rectal temperatures above 39.5°C or mucopurulent vulvar discharge characterizing postpartum dysgalactia syndrome (PPDS). *Number of initial piglets was standardized (n=14) for both treatments.
SE= Standard error.

Advances in the combined actions of genetics, management, health, and nutrition have resulted in hyperprolific females. Thus, the integrity of the mammary complex and adequate milk production, including the prevention of postpartum disorders, are of increasing importance for the proper development of piglets. Several studies have been conducted to minimize the harmful effects of postpartum disorders. The multifactorial scenario of PPDS causes, which are commonly noninfectious and subclinical, makes PPDS diagnosis difficult and justifies a prophylactic approach. In addition to the production aspect, prophylactic treatment with tolfenamic acid also addresses the concept of animal welfare, as farrowing is a painful process that generates pain and stress in the sow (Mainau et al., 2012). The use of anti-inflammatory therapies to improve pig welfare has also been reviewed (Bradbury et al., 2016; Schoos et al., 2019).

Some studies have reported that when combined with antibiotics, NSAIDs can aid in the treatment of the infectious causes of PPDS (Tummaruk & Sang-Gassanee, 2013). In the present study, tolfenamic acid had no effect on the occurrence of PPDS; however, we did not use tolfenamic acid in combination with other medications. Considering the subclinical forms of PPDS, Sabate et al. (2012) reported a reduction in piglet mortality with the use of ketoprofen plus amoxicillin. Buzato et al. (2006) suggested that sows exhibiting urinary problems before entering farrowing facilities are more likely to experience peripartum disease. Similarly, sows with urocystitis are more likely to develop simultaneous endometritis. These data suggest a correlation between urinary tract infections and peripartum diseases (e.g., PPDS).

Among the non-infectious causes of PPDS, pain and discomfort in the mammary system reduce milk quality and production and subsequently, the intake of colostrum and milk by piglets (Peltoniemi & Oliviero, 2014). Some studies suggest the positive effect of NSAID administration in mitigating effects in the postpartum disorders (Kotowski & Żmudzki, 2007; Mainau et al., 2016).

Like all NSAIDs, tolfenamic acid reduces prostaglandin synthesis and acts as an inhibitor of cyclooxygenase enzymes (COX) that increases after cell damage (Novotný et al., 2015). We found that the prophylactic administration of tolfenamic acid in gilts had a positive effect on litter performance. One explanation for this effect is the reduced stress and breast pain experienced by gilts during the postpartum period. This improved welfare could increase the receptivity of gilts to piglets and promote adequate milk intake, which contributes to improved performance and survival of piglets.

Table 3 shows that the initial average weight of piglets and the presence of diarrhea in the litter had significant effects on litter weight ($p < 0.05$). Several studies have provided insights into the effects of piglet birth weight until weaning (Blavi et al., 2021; López-Vergé et al., 2018a) and slaughter (López-Vergé et al., 2018b), showing a relationship between birth weight (Blavi et al., 2021) and diarrhea occurrence (Wang et al., 2019; Xiong et al., 2019) directly affecting litter weight at weaning (Table 3).

Table 3
Descriptive levels of probability for the effects of initial piglet weight (g), genetics, tolfenamic acid, genetics x treatment, diarrhea1, and diarrhea x treatment on piglet weight variables

Parameters	Birth weight (g)	Breed	Tolfenamic acid	Genetics x Trat.	Diarrhea[1]	Diarrhea x Trat.
Piglet birth weight (g)	-	<.0001	0.7909	0.2764	-	-
Piglet weight – 4 days old (g)	<.0001	0.1776	0.8333	0.0919	<.0001	0.1331
Piglet weight – 18 days old (g)	<.0001	0.3433	0.5673	0.0621	<.0001	0.8386
Litter weight – 4 days old (kg)	<.0001	0.1028	0.7745	0.3215	<.0001	0.0341
Litter weight – 18 days old (kg)	<.0001	0.3440	0.1093	0.1967	<.0001	0.0046
Litter average weight gain (kg)	<.0001	0.3440	0.1093	0.1967	<.0001	0.0046

[1] Diarrhea from 1- to 18-day-old piglets. Trat. = Tolfenamic acid.

When analyzing the effects of applying tolfenamic acid to sows and their litters, Kotowski and Żmudzki (2007) observed greater daily weight gain in litters of females treated with this NSAID. Positive treatment effects were also observed on the subsequent reproductive performance of females in the treatment group. Increased average daily weight gain has also been reported with the use of meloxicam (both intramuscular and oral), especially in piglets with low birth weight (Mainau et al., 2012, 2016). In contrast, Ison et al. (2017) did not observe any improvement in litter performance with ketoprofen administration.

The average incidence of diarrhea in the litter during the evaluation period is presented in Table 4. No significant differences in the incidence of diarrhea were observed between the tolfenamic acid and control groups ($p > 0.05$). A total of 71.6% of piglets in the control group had diarrhea from days 1 to 18, and the litter presented 21. 93% diarrhea incidence (>30% piglets affected), while the treated group showed 70.70% piglets and 27.39% litters with diarrhea ($p>0.05$).

Table 4
Incidence of diarrhea (mean ± SE) in piglets according to treatment (control vs. tolfenamic acid)

Parameters (%)	Control (n = 162)	Tolfenamic acid (n = 157)	$Pr>\chi^2$
Diarrhea at 1 to 4 days old (%)	53.09 ± 3.93	52.23 ± 4.00	0.9318
Diarrhea at 5 to 18 days old (%)	47.53 ± 3.94	42.04 ± 3.95	0.3120
Diarrhea at 1 to 18 days old (%)	71.60 ± 3.55	70.70 ± 3.64	0.8568
Overall diarrhea in litter (>30% piglets)	25.93 ± 3.45	27.39 ± 3.57	0.6966

Notably, primiparous gilts are more susceptible to postpartum disorders than multiparous sows (Tummaruk et al., 2010; Tummaruk & Sang-Gassanee, 2013). Owing to their low immunity, gilts are the most susceptible to diarrhea in their litter (Devillers et al., 2007), especially during the first week of life. A prominent effect of diarrhea at the expense of average (piglet and litter) weights and high mortality rates was observed in the present study (Table 5).

Table 5
Logistic regression model for piglet mortality at 4 and 18 days old

Parameters (%)	OR	CI (95%)		Pr>χ^2
Piglet mortality at 4 days old				
Tolfenamic acid vs Control	1.015	0.736	1.400	0.9266
Litter birth weight	0.999	0.998	1.000	0.0297
Piglet mortality at 18 days old				
Breed: B × A	1.027	0.740	1.424	0.8732
Tolfenamic acid × Control	0.709	0.521	0.964	0.0285
Diarrhea positive x Negative	1.129	0.824	1.547	0.4489
Treatments × Diarrhea:	-	-	-	0.0002
Tolfenamic acid × Control				
(No diarrhea)	0.387	0.226	0.662	0.0005
Tolfenamic acid × Control				
(Positive diarrhea)	1.298	0.950	1.775	0.1014
Diarrhea × No diarrhea				
(Control)	0.616	0.416	0.913	0.0157
Diarrhea × No diarrhea				
(Tolfenamic acid)	2.069	1.267	3.377	0.0036

OR= Odds ratio; CI= Confident interval.

The main cause of mortality in piglets was crushing, followed by weak piglets, with no difference between the evaluated groups. There was no effect of treatment on mortality among the 4-day-old piglets (p = 0.9266), with a mean of 4.5 in both groups. However, tolfenamic acid administration was effective in reducing mortality among 18-day-old piglets (p = 0.0285), with a reduction of 0.41% compared to the control group (6,733 ± 0.599 and 7,143 ± 0.721, respectively).

In contrast, tolfenamic acid had a positive effect on piglet mortality, even at high environmental temperatures. The effects of NSAIDs (e.g., flunixin) under thermal stress conditions have been observed by Tummaruk and Sang-Gassanee (2013). However, further studies are required to elucidate the

effects of NSAIDs on gilts and litters at high temperatures.

Table 5 presents the odds ratios of performance variables related to piglet mortality. Birth weight had an effect (p = 0.0297) on piglet mortality on the 4th day of life. The tolfenamic acid group had a lower mortality rate (OR = 0.709) on the 18th day of life (p = 0.0285) than the control group. Similarly, in litters without diarrhea, the treatment group had a lower mortality rate (OR = 0.387) on the 18th day of life (p <0.05) than the control group.

In the present study, piglet mortality was most influenced by the crushing of gilts and weak piglets. Moreover, tolfenamic acid positively affected piglet mortality at 18 days of age. Regardless of treatment, the incidence of diarrhea was high. *Escherichia coli* is the main etiological agent of neonatal piglet diarrhea, which is favored by the imbalance between immunity passed on by sow and the challenge posed by environmental contamination by pathogenic strains of this bacterium (Carney-Hinkle et al., 2013). While several risk factors are related to this pathology, the main ones include female immunity, inadequate environmental conditions, increased infection pressure, and the circulation of employees between rooms with pigs of different ages (Takeuti et al., 2019).

The positive effects of NSAIDs in reducing piglet mortality have been observed in previous studies (Homedes et al., 2014), even under conditions of high PPDS incidence (Sabate et al., 2012). Hirsch et al. (2003) observed lower piglet mortality in groups treated with the NSAID meloxicam (14%) when compared to those treated with the NSAIDs flunixin (31.7%). However, some studies found no such positive effects of NSAIDs on piglet mortality (Ison et al., 2017; Mainau et al., 2012, 2016; Viitasaari et al., 2013).

Upon isolating the effect of diarrhea on litter performance, the mortality rates in animals unaffected by diarrhea were 4.3% and 8.8% in the treatment and control groups, respectively (p <0.05). These results indicate a positive effect of the treatment on litters that were not affected by diarrhea (Table 6).

The two breeds of gilts showed a significant difference in the effect on body temperature above 39.5ºC, the incidence of PPDS, and the occurrence of diarrhea. The gilts of breed B had a greater chance (OR = 1.892; CI = 1.010–3.102) of having a body temperature above 39.5 ºC, as well as, that of PPDS incidence (OR = 2.061; CI = 1.144–3.715) and diarrhea (OR = 1.770; CI = 1.010-3.102) in litters aged 5 to 18 days (p = 0.0462).

Compared with gilts of breed A, those of breed B were 2.6 and 1.8 times more likely to have PPDS and temperatures above 39.5 °C, respectively. These factors may influence mortality during lactation. As the challenges of hyperprolificity increase, it is necessary to adjust the selection criteria to include characteristics related to predisposition to PPDS, total-born piglets, and neonatal survival (Edwards & Baxter, 2014).

Table 6
Effect of treatment (control vs. tolfenamic acid) and diarrhea on piglet and litter performance parameters

Diarrhea	Control (n = 162)	Tolfenamic acid (n = 157)	Mean	Pr>F
Piglet average weight at 4 days old (g)				
Positive (151)	1937.6±16.2	1955.7±16.0	1946.6±11.4	0.4254
Negative (168)	1854.8±16.3	1829.3±16.4	1842.1±11.7	0.2659
Mean	1896.2±12.6	1892.5±12.5		0.8333
Litter weight at 4 days old (kg)				
Positive (151)	26.03±0.30	26.50±0.29	26.27±0.21	0.2569
Negative (168)	24.99±0.30	24.33±0.30	24.66±0.22	0.1183
Mean	25.51±0.23	25.42±0.23		0.7745
Piglet mean weight at 18 days old (g)				
Positive (151)	4923.4±74.2	4974.5±73.9	4949.0±52.6	0.6242
Negative (168)	4579.9±51.9	4607.4±51.8	4593.7±37.1	0.7049
Mean	4751.7±49.3	4791.0±48.8		0.5673
Litter weight at 18 days old (kg)				
Negative (92)	62.33±1.18	66.69±1.17	64.51±0.83	0.0086
Positive (227)	60.42±0.82	59.55±0.82	59.98±0.59	0.4480
Mean	61.38±0.78	63.12±0.77		0.1093
Litter total weight gain (kg)				
Negative (92)	43.99±1.18	48.35±1.17	46.17±0.83	0.0086
Positive (227)	42.08±0.82	41.21±0.82	41.64±0.59	0.4480
Mean	43.04±0.78	44.78±0.77		0.1093

Conclusion

The administration of tolfenamic acid prophylactically to gilts after the farrowing of suckling piglets improved piglet performance but did not affect the occurrence of PPDS in primiparous sows.

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