Influence of a single-dose analgesic in sows post-partum on piglet growth and IgG level.

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Abstract

The amount of colostrum newborn piglets ingest in the first 24h after birth is of vital importance for their growth and the development of their immunity system during the first weeks of life. Colostrum does not only provide them with a high dose of energy and nutrients but contains a very high concentration of IgG antibodies as well. Treating post-partum sows with an analgesic might enhance the sow's welfare and hence enlarge the amount of colostrum intake by its piglets. In this clinical trial, the influence of injecting a single dose Meloxicam (Novem®) to farrowing sows post-partum on piglet bodyweight and serological IgG concentration is studied. Sows included (n=30) farrowed at the same day on the same farrow-to-finish farm in The Netherlands and were divided into two groups, a trial group (n=12) that received Meloxicam 20mg/ml (Novem®) and a control group (n=18) that did not receive any treatment. In the larger part of the litters, the piglets received an individual ID number, this enabled paired analysis on weight data from different points in time for 129 control and 120 trial piglets. Piglets were weighed at days 3 and 18 and serological IgG concentrations were quantified in 249 piglets at day 3 using Pig IgG ELISA (Bethyl Laboratories®). All data on weight and IgG-titre were analysed with SPSS21 Mixed ANOVA. The weight at 3 days appeared to be significantly (p=0,002) higher in the Meloxicam treated group (mean 1,88kg) than in the control group (mean 1,70kg). However, the observed higher mean on day 18 (trial:5,54kg, control:5,53kg) was not significantly different (0,234). The logIgG-values on day 3 (trial:4,54, control:4,10) were also not significantly different (p=0,099) between the two groups. Finally, as piglets might benefit from the analgesic in being able to ingest more colostrum, less spread of IgG titres within these litters could be expected. In this study, the variation coefficient did not appear to differ significantly (p=0,051) between the trial (VC=18,7%) and control (VC=29,8%) group. However, the p-value being below 0,1 did show a strong statistical trend towards significance. In conclusion of these results, administering Novem® to post-partum sows enlarges piglet weight at 3 days of age, possibly due to the intake of an enlarged amount of colostrum. This difference in weight did not show to be consistent in time, no significant differences could be found by day 18. As for piglet IgG titres, treatment led to two statistical trends to significance, the first in enlarging IgG concentration and secondly in lowering the variation of IgG titres within trial litters.

Abstract Dutch

De mate van biestopname door pasgeboren biggen in de eerste 24uur is van essentieel belang voor de groei en immuun status in de eerste levensweken. Biest bevat naast energie en essentiële voedingsstoffen ook een zeer hoge concentratie IgG antilichamen. Het post partum behandelen van zeugen met een pijnstiller verhoogd het welzijn van de zeug en daarmee de kans voor biggen om voldoende colostrum te drinken. In deze veldstudie is gekeken naar de invloed van een eenmalige toediening van de pijnstiller Meloxicam (Novem®) aan zeugen postpartum op biggewicht en serum IgG-waarden. In deze studie zijn 30 op één dag werpende zeugen op één vermeerdingsbedrijf in Nederland verdeeld in een behandelgroep (n=12) en een controlegroep (n=18), welke geen behandeling kreeg. Door het toewijzen van individuele ID nummers aan biggen in het grootste deel van de tomen waren gepaarde data voor gewicht in tijd bekend voor 129 biggen uit de controle- en 120 biggen uit de behandelgroep. De biggen werden gewogen op 3 en 18 dagen leeftijd en de serologische IgG titer bepaald op 3 dagen leeftijd met behulp van de PigIgG ELISA (Bethyl Laboratories®). De data van gewicht en de IgG-waarden zijn met behulp van SPSS 21 Mixed ANOVA geanalyseerd. Het gewicht op dag 3 bleek significant (p=0,002) hoger te zijn in de behandelgroep (1,88kg) ten opzichte van de controlegroep (1,70kg). Desondanks bleek het hogere gemiddelde gewicht op dag 18 (behandeld:5,54kg, controle:5,53kg) niet significant verschillend (p=0,234). De IgG-waarden op dag 3 (behandeld: 4,54, controle:4,10) lieten geen significant (p=0,099) verschil, maar wel een trend, zien. Door toediening van een pijnstiller zou een meer optimale biestvoorziening

voor biggen verwacht kunnen worden en hierdoor ook een lagere spreiding van IgG-gehalten binnen de tomen van behandelde zeugen. De variatiecoëfficiënt (VC) van logIgG binnen en tussen de tomen is geanalyseerd. Ui t de resultaten blijkt dat de variatiecoëfficiënt niet significant (p=0,051) verschilt tussen de Novem- (18,7%) en controlegroep (29,8%). Gezien de p-waarde onder de 0,1, mag wel gesproken worden van een statistische trend en lijkt de behandeling invloed te hebben op de mate van spreiding van antilichaam titers binnen de toom. Concluderend, de resultaten geven een positieve invloed van het toedienen van Novem® aan post-partum zeugen op het gewicht van biggen op dag 3, mogelijk veroorzaakt door een verhoogde biest opname. Dit verschil bleek niet consistent in de tijd, op 18 dagen was geen significant verschil in gewicht meer te vinden. Op de serum concentratie van IgG, liet de bahandeling alleen twee statistische trends zien. De eerste was een verhoging van de serum IgG waarde, de tweede een verlaging van de variatie in IgG concentraties binnen de behandelde tomen.

Introduction

The intake of colostrum is of vital importance for new-born piglets. A piglet is born with limited sources of energy and without adequate immune protection.[1] Therefore the intake of a sufficient amount of high quality colostrum is a necessity for gaining energy and passive immunity. During the first 12-36 hours[2] of life, the piglets intestines are permeable for large protein structures. This permeability declines by half during the first 12 hours post-partum.[3,4] Immunoglobulin's are large protein structures and are thus only able to pass the piglets intestinal barrier for limited time.

The immunoglobulin fraction in swine colostrum forms up to 80% of the total amount of proteins present and is composed of approximately 70-80% (mean 76%) IgG.[5] These levels have been shown to decrease by half in the first 12 hours post-partum[6]. Colostrum represents the only source of maternal antibodies for the piglet, as the swine's epitheliochondral placenta is impermeable to almost all immunoglubulins.[7]

An optimal distribution of colostrum among all piglets in a litter improves the litters health status and might lower the amount of piglet mortality. The challenge faced by contemporary intensive piggeries is to achieve this optimal distribution while sows' colostrum production does not keep up with the enlargement of litter size due to genetic selection. Additionally, not all sows are able to produce the same amount and quality of colostrum. Previous research revealed colostrum production to vary between 1,91kg and 5,31kg with averages of about 3,67kg.[4,8] The amount and composition of colostrum produced can be influenced by sow as well as litter characteristics, the sow's endocrine status, quality of nutrition, environmental factors or a combination of these.[9,10] Litter size however was found not to influence piglet growth or total production of colostrum during the first day postpartum.[10,11] It is important though to realize that the amount of colostrum per piglet decreases with 22-42gr per additional piglet born above a litter size of 12 piglets.[10,11] But, as Milligen et al showed, the influence of litter size on body weight might only become evident by day 21 and not at an early stage.[12]

There has been limited research on the influence of analgesics on the distribution of colostrum among piglets. Administration of an analgesic post-partum has shown a tendency to reduced sow discomfort and a decreased number of body position changes. This is thought to reduce the number of piglet being crushed. But as stated by the authors of this study, utilization of better adjusted crates or an increase in sow body fat may be more practical solutions to prevent piglet crushing.[13,14] Reduction of changes in body position however might enable the piglets to suckle for longer times, as might injecting Meloxicam within two hours after farrowing to enlarge total time lying of the sows.[13] Viitasaari et al showed several additional benefits for the administration of NSAID's post-partum on

sows welfare. Treated sows showed less rapid decrease in body condition scores and less moments of feed refusal compared to sows in the control group.[15] An optimal body condition and sufficient feed intake are key factors in the sow's ability to produce sufficient amounts of milk to benefit piglet growth. Apart from body condition and feed intake, the sow's general health status post-partum is also of great influence on its ability to produce enough colostrum. With longer farrowing duration, some sows tend to get feverish the first day after giving birth, a tendency that appears to be most frequent at lower parities. Admitting NSAID's to those sows showed to reduce their fever and thus improve their health and welfare.[16]

Although not proven, one might think of several other advantages of administering an analgesic to sows post-partum. Reduction of pain and stress post-partum might benefit hormonal stability and the right onset of colostrum/milk production peripartum, hence leading to larger amounts of colostrum. The improved welfare might allow the sow to tolerate her piglets to suckle for longer time, thus an increase in colostrum intake. Piglets provided with sufficient amounts of colostrum will show enlarged growth rates and better immunity. This increases the overall health status on the farm and provides economic benefits in reaching higher slaughter weights and less mortality.

In this study, the analgesic Novem® was used. Novem (Boehringer-Ingelheim AB), consisting of meloxicam and ethanol, is licensed in the Netherlands for pigs, cattle and horses. Meloxicam belongs to the oxicam class and acts, by inhibiting prostaglandin synthesis and COX-2, anti-inflammatory, analgesic, antipyretic and antitoxic. In Europe it can be used to treat non-infectious locomotor disorders and postoperative pain relieve by soft tissue surgery in swine.[17,18]

The aim of this study was to determine the influence of injecting a single dose of the analgesic Novem® post-partum in farrowing sows on the bodyweight and IgG levels of their piglets.

Materials and methods

Materials

Origin and selection

This study was performed at a 1400 sow farrow-to-finish farm in The Netherlands. This farm was chosen because its ability to deliver enough sows, for both the trial and control group, farrowing on the same day. On this farm, induction of parturition was routinely performed on day 115 of gestation by injection of prostaglandin analogues, later followed by an injection of 1mL of oxytocin (Oxytolint®). Sows that had farrowed during the night (12pm-6am) were allocated to the trial group. Sows farrowing after 6am on day 0 were assigned to the control group. Sows in the trial group (n=12) received 5 ml of Novem®(2mL/100kg) IM, whereas those assigned to the control group (n=18) did not receive any treatment. Postpartum, all litters were adjusted to a size of about 11-14 piglets. Piglets of sows with larger litters were transferred to sows with smaller litters. At this farm a system of coloured pins indicated whether a sow still had only her own piglets (green pin), if some piglets were added to the litter (blue pin) or if all piglets in the litter originated of other sows (red pins). The two groups were housed in the same compartments and received the same amount and quality of care. All farrowing crates were provided with a chart that was used to note additional parameters such as birth assistance, amount of piglets born alive and dead, percentage of piglet mortality during lactation and any occurring additional problems.

On day 3 the piglets from sows in the trial group were provided with a red ear tag as those in the control group got a green ear tag. Additionally, the litters of 9 sows from the trial group and 10 sows of the control group were selected for blood sampling and individual weighing of the piglets. Selection criteria included comparability in litter size and parity number, the presence of healthy litters and preferably unchanged litters (green pin). All piglet of these sows (n_{Novem}=120 (9 litters)),

$n_{Controle}$=129 (10 litters)) were tagged with an individual ID-number, to determine their individual serological IgG status and their weights on days 3 and 18.
The piglets in the non-selected litters (n_{Novem}=38 (3litters), $n_{Controle}$=110 (8litters)), were individually weighed at day 3 and day 18 as well, but these data could not be paired since no individual ID numbers were known.
At week 9, most the piglets seemed to be replaced but they could be traced back to one of the two groups by the colour of their ear tag. The piglets were weighed per litter and per ear tag colour. Unfortunately, these weights could not be analyzed properly since no individual data, no information on litter of origin and no individual weights were known. It was therefor decided to leave these data out of consideration in this paper.

Methods

Piglet body weight

On day 3 and day 18, all piglets in each litter were weighed individually. As mentioned above, only the weight at day 18 of those piglets with individual ID number could be linked to a weight for that particular piglet at day 3.

Piglet serological IgG

The blood samples of the 249 piglets were analysed by an enzyme-linked immunosorbent assay (ELISA) (Pig IgG ELISA, Bethyl Laboratories®) at the laboratory of veterinary clinic 'De Lintjeshof' in Roermond, The Netherlands. The assay was performed according to the manufacturer's instructions.

Statistics

All data were analyzed using IBM SPSS statistics 21.
As showed in figure 1, the data on weight at day 3 and day 18 displayed a normal distribution. The data on serological IgG concentrations needed to be log-transformed.

Data were analyzed using a Mixed ANOVA model, with the input shown in figure 2.
Firstly, separate analyses were performed for weight at day 3 and day 18 and logIgG, respectively. Secondly, the assumption of paired data was taken into account. In this second analysis, only piglets with a unique ID number could be included, since, as mentioned before, only they provided paired data.

After these main analyses, a mixed ANOVA using litter means was performed using paired data. In this analysis, litters without individually identified piglets could be included as well.

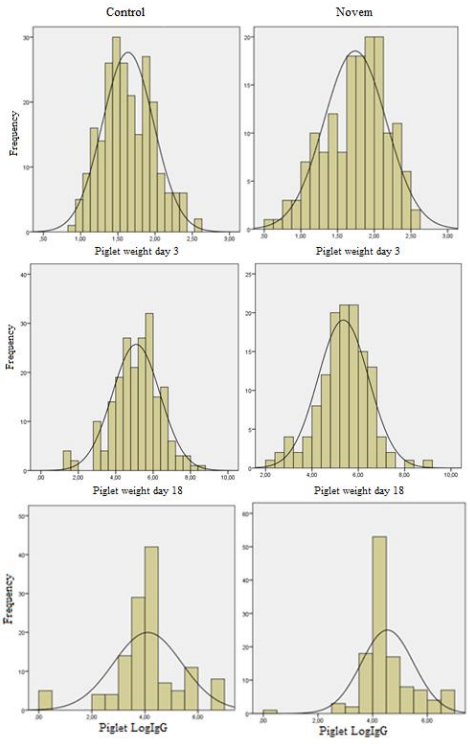

Figure 1: Distribution of collected piglet data on weight day 3, weight day 18 and logIgG.

There have been suggestions that piglets with the lowest birth weights may benefit the most from their dam being treated with an analgesic like Novem[13]. Therefore, the lowest quartile of the piglets in weight on day 3 were analyzed in a separate analysis. This group consisted of 99 piglets (n_{Novem}=34, $n_{Controle}$=65). Since paired data were needed for this model, only those piglets with an individual ID number could be included, this left 34 piglets to be analysed (n_{Novem}=11, $n_{Controle}$=23).

Finally, some litters showed problems during farrowing. A total of 8 litters on day 3 and 10 litters at day 18 had remarks on their chart. Examples of the nature of these remarks were diarrhoea, an unexpected low growth rate and one of the sows suffered from an anus prolapse due to giving birth. Since this might all be factors interfering with the results, a sensitivity analysis was performed to estimate the effect on the results of this study. None of the litters showed values outside the 95% prediction interval, but there were 5 litters showing values outside the group mean +/- 1x standard deviation. A mixed ANOVA excluding these litters was performed as described above.

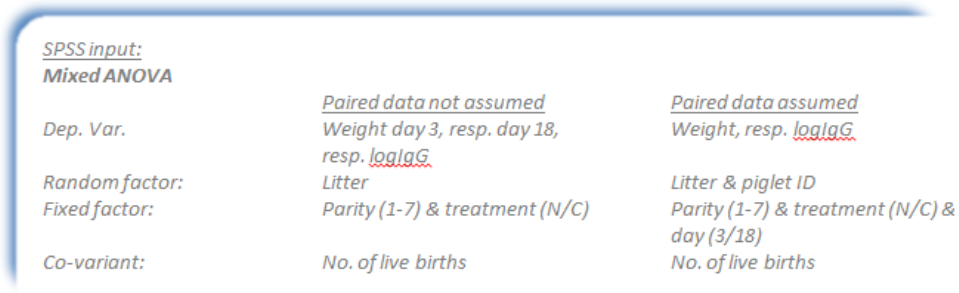

Figure 2: SPSS Mixed ANOVA input shown for the two main analysis performed.

The Variation coefficient for IgG titres was calculated by SPSS by dividing the standard deviation by the mean of each litter separately and all litters per group combined.

VI Results

Effect of Novem® on piglet weight

The results of the paired analysis on piglet data as shown in table 1, show a significant difference in weight between the groups at day 3 (p=0,002) as well as for parity (p=0,000) (see table 3). Weight at day 18 appears not to be significantly different (p= 0,234). The estimated differences can be seen in table 2.

Mixed ANOVA on paired individual piglet data on weight

Parameter	Treatment	N	Mean	st.dev	st.error
Weight day 3	Novem	120	1,8786	0,33640	0,03071
	Control	129	1,7006	0,30452	0,02681
Weight day 18	Novem	97	5,5377	1,02363	0,10393
	Control	126	5,5292	1,04889	0,09344

Table 1 (left): Results of the paired analysis of individual piglet data on weight.

Paired analysis estimates

Parameter	Estimates
Day 3	-3,6337
Day 18	0
Novem: Day 3	0
Control: Day 3	-0,0319823
Novem: Day 18	0
Control: Day 18	-0,127452
Parity 5	-4,44738
Parity 7	0

Table 2: Estimates of table 1

Paired analysis significance

Source	Significance
Day	0,000
Treatment (N/C)	0,011
Treatment Day 3	0,002
Treatment Day 18	0,234
No. Of live births	0,048
Parity (1-7)	0,000
Parity 5	0,023

Table 3: Significance of table 1

The independent analysis of individual piglet data (results not shown) revealed similar results with a significant difference in weight between the groups at day 3 (p=0,035) and none at day 18 (p=0,234). Paired analysis performed on litter means for weight did show differences in average means at day 3 (trial: 1,7493kg, control: 1,6394kg) and day 18 (trial: 5,3558, control 5,0065kg), but weight did not appear to differ statistically significant (p=0,101). The number live births (p=0,005) en parity (p=0,071) showed a statistical trend towards significance for litter mean body weight.

Analysis on the quartile of piglets with the lowest bodyweight at day 3, the ones that might benefit most from treatment, revealed no significant (p=0,537) differences in bodyweight between the trial (1,2291) and control group (1,2887). Parity appears to have a statistical trend towards significance (p=0.074) for bodyweight
Excluding selected litters (showing means outside the mean+/- 1x std. dev.) did not change the overall conclusion, the weight at day 3 still was significantly different (p=0,003) between the groups as the weight on day 18 still showed no significant difference (p=0,132 and p=0,171).

Effect of Novem® on IgG-titre
The results of the analysis on individual piglets logIgG as shown in table 4, show no significant differences in logIgG between both groups (p=0,099) , although the p-value being below 0,1 might indicate a statistical trend towards significance (see table 6). Parity does show to have a significant influence on logIgG (p=0,011) while number of live births does not (p=0,942). The estimated differences can be seen in table 5.

Mixed ANOVA on individual piglet IgG

Parameter	Treatment	N	Mean	st.dev	st.error	VC
LogIgG	Novem	120	4,5405	0,95626	0,08729	21,1%
	Control	129	4,1046	1,28826	0,11342	31,4%
LogIgG -> IgG	Novem	120	93,7377			
	Control	129	60,6185			

Table 4 (left): Results of the analysis of individual piglet data on IgG titres.

Analysis estimates

Parameter	Estimate
Treament control	-0,26927
Treatment Novem	0
Parity 2	-0,679259
Parity 6	-1,04651
Parity 7	0

Table 5: Estimates of table 4

Analysis significance

Source	Significance
Treatment (N/C)	0,099
No. Of live births	0,942
Parity (1-7)	0,011
Parity 2	0,081
Parity 6	0,007

Table 6: Significance of table 4

The analysis on litter means of logIgG did show differences in average means between the trial (4,9359) and control group (4,6994), but this did not appear to differ statistically significant (p=0,962). The number live births (p=0,159) and parity (p=0,113) both showed no significant influence on IgG concentrations.

Analysis on the quartile of piglets with the lowest bodyweight at day 3 revealed no significant (p=0,0746) differences in LogIgG titres between the trial (4,2282) and control group (4,1164). Parity appeared to have a significant influence (p=0.001) on LogIgG.
Excluding litters did not change the analysis since none of the piglets in these litters had registered IgG concentration.

An independent-sample T-test revealed no significant difference (p=0,051)between the litter mean variation coefficients on logIgG values. Although this difference is not significant, one might interpret this as a statistical trend towards significance. Figure 3 shows the litter mean variation coefficients within litters between treatment groups.

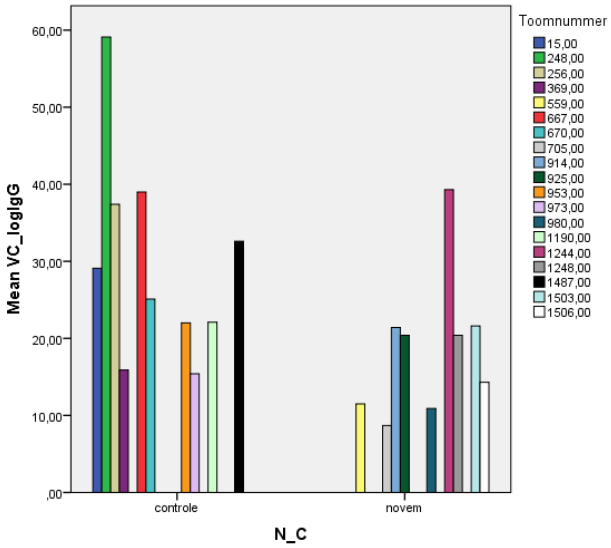

Figure 3: Litter mean variation coefficient (%) compared between the two treatment groups.

VII Discussion and conclusion

The aim of this study was to determine the influence of injecting a single dose of the analgesic Novem® post-partum in farrowing sows on the bodyweight and immunity status of their piglets. The results show the body weight at day 3 to be significantly higher in the trial group compared to the control group. Although both bodyweight at 18 days and IgG concentrations showed higher values in the trial group, those differences were not significant. In addition, there was a tendency showing within litter variation of IgG titres being lower in litters of trial sows, than in those of control sows.

In this study, the difference in bodyweight at day 3 is shown to be due to treatment. However, one essential factor to take into consideration is the uncertainty of equal body weight between the groups at the start of this study. Also, the mean number of parity of the control group (4,7) was higher than that in the trial group (3,3). Although there are no strong indications parity is of large influence on birth weight, this might still be a factor of concern.[19,20] First parity sows usually have smaller litters and weaker piglets. Quesnel et al showed litters of first and second parity sows to have a larger variation of bodyweight within litters.[21] The difference in bodyweight found in this analysis might therefore not be due treatment alone. Smith at al showed that piglets with higher birth weights will show higher weights at weaning and 42days after weaning as well.[22] This was not confirmed in our study. One reason might be the fewer number of observations at day 18 to reach significance, another might be that the difference in weight on day 3 in our study is indeed due to higher colostrum intake. Unfortunately, we were not able to show the benefit of that hypothesis in the weight of day 18.

One might wonder why the statistical difference in mean body weight at day 3 seems to be disappeared at day 18. As well as one may wonder why significant higher bodyweight in the trial group, likely derived from higher colostrum intake, does not automatically result in a significant higher result for serological IgG titres in this group. There may be several explanations for these two questions. The design of this study might have interfered with the results as it was the farmers choice which sows to select. Sows that gave birth at night were all assigned to the trial group, while those giving birth during the day ended up in the control group. Some sows receiving treatment might have given birth up to a maximum of 6 hours before receiving their treatment due to lack of supervision between midnight and 6am. The intestines of piglets start to be less permeable for immunoglobulin's after only 6 hours. Consequently, even if colostrum intake of the piglets was higher due to treatment

compared to those being born in a control litter, the benefit of ingesting more immunoglobulin's might not be proportional to that of energy intake. Another point of concern is the amount of analgesic injected, all sows in the trial group received the same amount regardless their actual weight; 5mL, a dosage for swine of 250kg. This might interfere with the results as those sows under- or overdosed will show less accurate results than could be expected when injected with the right dosage. Another disturbing factor in this study was the fact that not all sows nourished their own piglets. In this analysis this factor is left out of consideration under the assumption that piglets were transferred to their adoption sow within 24hours, being within the intestinal closure time. We did however include the variable of the number of live births of each sow, in case the piglets in large litters were removed after they already had their share of colostrum. At day 18, some piglets were transferred to other litters or disappeared at all. Unfortunately, it is not known what happened to these piglets and if their weight might have been of influence on their transfer or disappearance. This might have influenced the results, as less data were known at day 18 and litter means might not be complete trustworthy if having a high or low bodyweight has been the reason for transfer or disappearance.
A final remark on this study should be made on the weight overall. Although no problems occurred on the farm during this study, the weight of the piglets was below expectation.

Although a field study will always be influenced by more factors than one could account for, some adjustments in the study design should be encountered to achieve more trustworthy results on the influence of this analgesic on piglet growth and immunity. Preferably, the study would have a double-blind design to ensure no bias in selecting the sows for both groups. Secondly, there should be an accurate administration of piglet mortality or reasons to transfer piglets to other litters. Since the main interest of this study is the development of weight, all piglets should be provided with an individual ID number, only litters with the sow's own piglets should be included and data on birth weight should be collected. In this study the amount of litters in both groups were not equally divided, resulting in a smaller trial group. Ideally, both treatments are resembled by an equal amount of groups with an equal amount of piglets to improve precision. In this study the difference in IgG variation coefficient between the treatment groups did show a trend toward significance but no actual significance. This might be due to the low number of observations.

Further research should be performed to achieve more representative results. These results will be of interest for commercial pig farmers, since the improvement of welfare of their sows might at the same time enable their piglets to grow faster and have a better immunity status resulting in economic benefits.

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