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Implications of nutritional modulators in productive performance of pregnant and lactating sows

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ABSTRACT

A meta-analysis was conducted with the aim to assess the use of nutritional modulators and their effects on reproductive performance of pregnant and lactating sows. Bibliographic data, experimental characteristics, and types and levels of nutritional modulators were tabulated. A total of 22,608 sows from 68 studies, published between 1989 and 2017, were included in the meta-analysis. This analysis was conducted sequentially via a graphical, correlation and variance analysis. There was no significant difference ($P > 0.05$) between the average feed intake and body condition of sows in groups supplemented with L-carnitine, chromium, and somatotropin. L-carnitine and chromium supplementation in pregnant sows was found to increase the number of live-born piglets by 2.3% ($P < 0.05$) and 4.7% ($P < 0.01$), respectively. Piglet weights were 5.5%, 2.8% and 3.4% higher ($P < 0.05$) in L-carnitine-, L-arginine-, and somatotropin-supplemented sows than those in the control sows. Somatotropin administration increased the number of weaned piglets by 9.0% ($P < 0.05$). Responses of body condition of sows to supplementation and the nutritional composition of diets were poorly explored in studies with nutritional modulators, which makes it impossible to reach conclusions about the efficient use of these additives for nutritional adjustments in pregnant and lactating sows. In summary, the performance of litters can be improved in sows supplemented either with L-carnitine, L-arginine, chromium or somatotropin, during gestation and lactation.

1. Introduction

Prolific sows have an increased nutritional demand, and thus a lower piglet weight at birth and a higher neonatal mortality rate (Martineau and Badouard, 2009). To mitigate these effects, mechanisms to improve female nutritional intake and productive and reproductive indices have been continuously researched and applied in intensive production systems.

Among the nutritional modulators that influence sow performance, L-carnitine, L-arginine, chromium, somatotropin and ractopamine have the highest available studies. Based on the volume of this information already published, meta-analysis becomes an excellent tool for integrating the main responses of these modulators. L-carnitine, L-arginine and chromium act as performance enhancers, because they alter the energy partition and nutrient flow at the placental and tissue levels (Dallanora et al., 2017; Lindemann and Lu, 2018). Administration of somatotropin during pregnancy increases the litter size and piglets' weight at birth (Gatford et al., 2010). Ractopamine is believed to improve body condition of the sows and result in a greater uniformity and weight of piglets at birth, which guarantee a higher growth rate of piglets and milk production (van Wettere et al., 2016). However, ractopamine is used as a commercial feed additive only in Brazil, the USA, Australia, Canada and Mexico.

Currently, the use of ractopamine and somatotropin is in discussion worldwide, mainly due to insufficient evidence regarding the risks associated with their constant use on human health. Around 160 countries, including the entire EU, China and Russia have banned the administration and import of pig products treated with ractopamine and somatotropin (Alemanno and Capodieci, 2012; Pacelle, 2014; Dunshea et al., 2016). Furthermore, the supplementation of livestock diets with trivalent chromium has been banned in EU countries, due to ambiguity in test results (Dunshea et al., 2016).

Examples of both positive and negative results of the use of nutritional modulators in pig production are available in literature. The integration of information regarding the use of nutritional modulators (L-carnitine, L-arginine, chromium, somatotropin and ractopamine) is challenging, due to the variability in research conditions, and the effects of using individual or combined additives on the performance of

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pregnant sows and their litters. Thus, the present study aimed to integrate this information and assess the impact of dietary modulators on productive performance of pregnant and lactating sows, through a meta-analysis.

2. Materials and methods

2.1. Systematization of information

Indexed publications based on in vivo experiments on sows fed diets supplemented with nutritional modulators were selected from the search engines Elsevier, Science direct, Scopus, Scielo, PubMed, Periodic CAPES, and Scholar Google. The keywords used for the search were: sows, nutrition, additives, L-carnitine, L-arginine, somatotropin, ractopamine or chromium, and were translated to several languages (English, Portuguese, Spanish, French and Italian). Based on the keywords searched, 145 publications were selected initially.

The main criterion for selecting the publications was the administration of nutritional modulators: L-carnitine, L-arginine, chromium, somatotropin or ractopamine in pregnant and/or lactating sows. Data on reproductive performance (birth of alive, dead, and mummified piglets), body condition (body weight, backfat thickness, maternal weight gain and weight loss), performance (feed intake, milk production), and piglet condition (weaning weight, weaned number) were also included. Additionally, a control group was established to make comparisons with the results of the groups supplemented with nutritional modulators. After selection, each article was evaluated critically for its quality and relevance to the objectives and criteria of this study. For selecting the technical bulletins, we considered the methodology and results presented, in addition to the published ISSN (International Standard Serial Number). The outcome of a single study (i.e., whether dietary modulator was beneficial or not) was not considered as a criterion for inclusion in this database. After sorting based on the selection criteria, the database consisted of 68 publications, of which 60 were scientific articles, 06 were dissertations and theses, and 02 were technical bulletins.

2.2. Database management, coding and data filtering

A database with information relating to each selected publication was created in an Excel (Microsoft Corporation, 2013) spreadsheet. The tabulated data included the bibliographic information (authors, year, journal, country, institution of origin), experimental characteristics (experimental design, type of dietary modulators, inclusion level in the diet, nutritional composition, days of experiment, lineage, parity order, phase [gestation and/or lactation], ambient temperature, body weight), and the variables tested (reproductive performance, feed intake, gain/loss/variation in backfat thickness, number of alive/dead/mummified piglets born, number of piglets weaned, and piglet weight).

The data were analyzed graphically to understand the distribution, coherence, and heterogeneity of the data. Through this analysis, hypotheses were established, and the statistical model was defined (Lovatto et al., 2007). The definition of dependent and independent variables and the codification of the data for analyzing inter- and intra-experimental effects was performed according to Lovatto et al. (2007) and Sauvant et al. (2008). Briefly, sequential numbers were used to encode each article (general encoding), each treatment within a study (inter encoding, i.e., each treatment received a sequential number and was concatenated to the previously given article code), and repeated measures for different time intervals or doses when available (intra encoding). Additional encodings were done to facilitate the graphical and statistical analyses of the database. In this study, encoding was attributed to the additives related to the control treatment for each article ('No' or 'Add'). In addition, encodes were inserted to classify experimental groups, and treatments were divided into six groups: control (sows that did not receive any additives), L-carnitine, L-arginine, chromium, somatotropin and ractopamine treatments.

2.3. Database description

The database included 82 experiments published in 68 publications, from 1989 to 2017 (mode: 2006), comprising of 22,608 sows, with a mean of 47 sows per treatment and 134 sows per study. Complete tables with the database information of each nutritional modulators are available in the Supplementary materials (Table S1-S5). Parity order of the sows was 2.39, with a variation of 1 in 6. The experiments consisted of a total of 524 experimental groups (T): control (224), L-carnitine (107), L-arginine (59), somatotropin (57), ractopamine (30) and chromium (31 and 16 combinations with analogues).

Majority of the experiments were carried out in American (34% of the articles), German (19%), Brazilian (18%), and Australian institutions (11%). In 56% of the selected publications, sows were housed in individual crates, in 18% of the publications, they were kept in a group housing system, whereas 26% of the publications did not report sow housing. The average available area per sow, reported in the publications, was 1.90 m^2 for accommodation in crates, and 2.60 m^2 in collective pens. The nutritional composition of experimental diets, with or without the addition of dietary modulators, is described in Table 1.

The level and duration of administration (mean values) of dietary modulators and somatotropin were calculated during gestation: addition of 1.14% of L-arginine in diet for 45 days, 90 mg/day of L-carnitine for 58 days, 363 ppm/kg diet of chromium for 75 days, 20 ppm/kg diet of ractopamine for 35 days, and 6 mg/day of somatotropin for 50 days. During lactation, dietary modulators were administered with the diets for an average duration of 23 days. The levels of dietary modulators and somatotropin were calculated (mean values) for lactating sows: 1.28% of L-arginine in diet, 150 mg/day of L-carnitine, 382 ppm/kg diet of chromium, and 15.8 mg/day of somatotropin.

2.4. Statistical analyses

Statistical heterogeneity was determined using the I^2 statistic, which describes the proportion of variance in cross-sectional studies that can be attributed to heterogeneity of the analysis, and a residue analysis was conducted to verify if normality and homoscedasticity were significant, according to the Anderson Darling test. In the analysis of heterogeneity, the random effects model was used for all dietary modulators. The Pearson correlation test was used to test the correlation between the continuous variables in the database. Dietary modulators were analyzed with the levels of supplementation in diets. The strength of correlation was interpreted following Mukaka (2012), where values greater than 0.7 indicated a strong relation, and those less than 0.5 indicated a weak correlation. Generalized linear models were employed for the analyses of variance and comparisons by Tukey test. The effect of each additive was contrasted with the respective control treatment for each study, hence, the means of the variables in the variance analysis are presented specifically for each additive, in the form of 'No' (control) and 'Add' (additive). The period of supplementation (beginning, middle, or end of gestation phase) and length (days of supplementation) were not tested due to limited data availability. Data were analyzed separately for the gestation and lactation phases. The publication number was fixed in all analyses to exclude possible random effects. The same model was used for all dietary modulators. Some factors were excluded from the analytical model for analysis of variance due to high variability (level and period of supplementation) or lack of information. The factors that did not indicate any statistical effects, e.g., parity order, lineage, sample size, and housing system, were excluded from the model.

To compare the levels of nutrients effectively provided of the studies and the animal requirements, the latest versions of the NRC (2012) and Brazilian tables for Poultry and Swine (Rostagno et al., 2011) were adopted to evaluate the appropriate nutritional recommendations.

Table 1
Mean of values of nutritional composition of experimental diets using dietary modulators and somatotropin administration (Add) or (No) for pregnant and lactation sows.

Experiments, n	Gestation[2] 14 L-car, mg/d		9 L-arg, %		2 Cr, ppm/d		11 pST, mg/d		5 Rac, ppm/d	
	No	Add	No	Add	No	Add	No	Add	No	Add
ME, MJ/kg	11.0[1]	10.8	13.2	13.1	13.3	13.3	13.1	13.3	13.1	13.0
CP, %	14.0	14.1	14.4	14.4	14.0	14.0	14.3	14.8	14.6	14.5
Lys, %	0.68	0.68	0.74	0.76	0.67	0.73	0.76	0.73	0.76	0.77
Met, %	0.22	0.22	0.31	0.28	0.54	0.54	-	-	0.25	0.25
Thr, %	0.44	0.44	0.58	0.60	-	-	-	-	0.63	0.63
Try, %	0.26	0.26	0.26	0.35	0.65	0.65	-	-	0.80	0.80
Ca, %	0.85	0.85	0.83	0.80	0.84	0.86	1.11	1.00	0.86	0.82
P, %	0.74	0.75	0.53	0.54	0.74	0.76	0.88	0.80	0.61	0.58
Experiments, n	Lactation[3] 11 L-car, mg/d		8 L-arg, %		3 Cr, ppm/d		2 pST, mg/d		1 Rac, ppm/d	
	No	Add	No	Add	No	Add	No	Add	No	Add
ME, MJ/kg	12.8	12.9	14.3	14.1	13.4	13.4	14.4	13.8	13.4	13.4
CP, %	17.6	17.7	16.1	14.2	14.1	14.6	17.0	18.2	-	-
Lys, %	0.93	1.39	0.95	0.85	0.93	1.01	1.06	1,00	-	-
Met, %	0.35	0.35	0.55	0.57	-	0.54	0.31	0.31	-	-
Thr, %	0.48	0.48	0.68	0.60	-	-	-	-	-	-
Tryp, %	0.17	0.17	0.20	0.20	-	-	-	-	-	-
Ca, %	0.94	0.93	0.95	1.00	0.82	0.89	0.92	0,92	-	-
P, %	0.84	0.83	0.59	0.52	0.73	0.77	0.76	0.76	-	-

L-car: L-carnitine, L-arg: L-arginine, Cr: chromium, pST: Somatotropin, Rac: Ractopamine,
No: diets without and Add: diets with nutritional modulators.
ME: Metabolizable energy, CP: Crude protein. Lys: Lysine, Met: Methionine, Thr: Threonine, Tryp: Tryptophan, Ca: Calcium, P: Phosphorus.
[1] Arithmetic mean of the values showed in the calculated nutritional composition of the experimental diets.
[2] Levels supplemented in gestation phase (minimum - maximum): L-car: 25 – 435 mg/d of L-carnitine; L-arg: 0.4 – 1.5% of L-arginine; Cr: 200 – 1000 ppm/kg diet of chromium; pST: 10 – 70 mg/d of Somatotropin; Rac: 20 ppm/d diet of Ractopamine
[3] Levels supplemented in lactation phase (minimum - maximum): L-car: 25 – 350 mg/d of L-carnitine; L-arg: 0.5 – 2.0% of L-arginine;
(n) number of experiments containing nutritional composition information.
- Dash (empty cells) indicate lack of information of the nutrient in the composition diets.

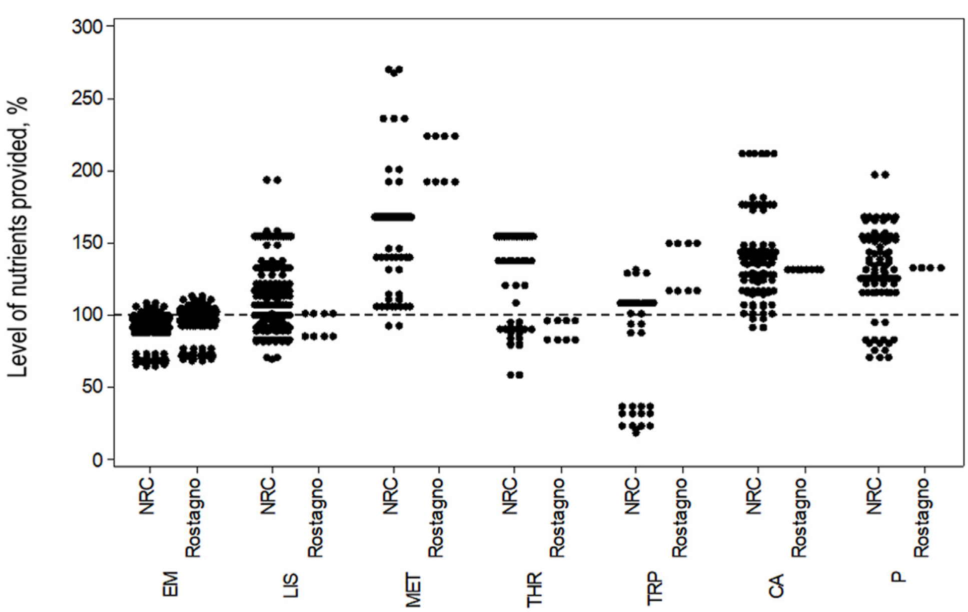

Figure 1. Relation between recommended levels of nutrients for multiparous sows (according to NRC (2012) and Brazilian Tables - Rostagno et al. 2011) and the levels effectively provided, expressed in percentage (%). Nutritional composition of diet (for example. PB, %/kg of diet) multiplied by 100, and divided by nutrient required in tables (NRC or Rostagno), expressed in same unit. Each point is a treatment in the database.

These two models consider body weight, weight gain and reproductive weight gain (uterus and mammary tissue) to meet the nutrient requirement of pregnant sows. Calculated nutrient composition expressed in diets in all experimental groups (database lines) were compared with the current nutritional recommendations estimated by the proposed models, according to parity order and gestational phase. The difference between the nutritional composition of diets in the studies and the nutritional recommendations of tables was individually expressed as a percentage variation in each treatment of the database showed in Fig. 1. This relation was estimated of values of nutritional composition of diet (for example. PB, %/kg of diet) multiplied by 100, and divided by nutrient required in tables (NRC or Rostagno), expressed in same unit. All analyses were performed using Minitab 16 software (Minitab Inc., State College, USA).

3. Results

3.1. Systematic analyses

According to the Higgins index, all nutritional modulators indicated high heterogeneity ($P < 0.01$) in the evaluated experiments: 85.8% for L-carnitine, 99.9% for L-arginine, 99.4% for chromium, 99.9% for somatotropin and 99.9% for ractopamine. Based on these values, we used the analytical model that prioritizes the random effects for each variable analyzed. The database included 82 experiments that involved supplementation of L-carnitine (22), L-arginine (19), sources of chromium (11), somatotropin (20) and ractopamine (10) for pregnant and lactating sows, selected according to the criteria established for meta-analysis. Out of the five modulators studied in this meta-analysis, ractopamine was used in the least number of experiments, and had the least information available for response variables.

Several obstacles were encountered in this meta-analysis due to the methodological variability between the experiments, and the lack of data on response variables in majority of the publications made it impossible to analyze deviation for some variables. Most studies that evaluated dietary modulators did not indicate the nutritional composition of diets. Some publications described mostly metabolizable energy levels, lysine, methionine, calcium and phosphorus: 14/22 L-carnitine, 09/19 L-arginine, 00/11 chromium, 10/20 somatotropin, 10/10 ractopamine (Table 1).

The average daily feed intake of sows during gestation and lactation was not reported in ractopamine experiments. Furthermore, it was not possible to analyze backfat thickness (BT), an indicator of the sows' body condition, at the final stage of gestation for L-arginine, chromium and ractopamine, as well as BT at farrowing for L-carnitine, chromium, ractopamine and somatotropin modulators. No information was available on body weight in articles involving chromium and ractopamine as dietary modulators (Table 2). Somatotropin administration in lactating sows was identified in only one study. Most experiments involving somatotropin were carried out in the gestation phase.

3.2. Body performance of sows

Performance of sows is shown in Table 2. No significant differences ($P > 0.05$) were observed for average daily feed intake during gestation and lactation, sow body weight at insemination, and backfat thickness at the initial and final stages of gestation for pregnant and lactating sows between the control groups and those receiving somatotropin or nutritional modulators. Pearson's correlations (r) between levels of nutritional modulators supplemented in diets and average daily feed intake and body condition of pregnant and lactating sows are shown in Table 3. No correlations ($P > 0.05$) were observed between dietary modulators (L-carnitine, L-arginine and chromium) or somatotropin administration and sow backfat thickness or sow body weight. Studies on chromium and ractopamine supplementation in sow diets did not provide information on sow body condition. Sows' feed intake during gestation was not correlated ($P > 0.05$) with somatotropin administration or diet supplementation with different levels of dietary modulators in pregnant sows. Feed intake increased with L-arginine levels in the diet during lactation ($r = 0.885$, $P < 0.05$). During lactation, the sow weaning weight and backfat thickness were not correlated with the dietary supplementation of L-carnitine or L-arginine.

3.3. Performance of sows and litters

Productive performance of litters of sows receiving somatotropin during gestation, or dietary supplementation during gestation or lactation are shown in Table 4. None of the tabulated studies evaluating L-carnitine supplementation reported the number of weaned piglets and weaning weight (Tables 4 and 5). The total number of mummified piglets, as well as the weight at weaning, were present in one article on chromium supplementation. Only one study that evaluated the effect of ractopamine on sows indicated the total number of piglets. L-carnitine and chromium supplementation in pregnant sows increased the number of live-born piglets by 2.3% ($P < 0.05$) and 4.7% ($P < 0.01$), respectively. The number of stillborn and mummified piglets was 24 and 80% higher ($P < 0.05$), respectively, in control sows than among those receiving L-arginine-supplemented diets during gestation. Piglet weight at birth was 5.5%, 2.8% and 3.4% higher ($P < 0.05$) in L-carnitine- and L-arginine-supplemented sows and those administered somatotropin, respectively, than that in control sows.

Pearson's correlations (r) between piglet performance and dietary supplementation in lactating sows are shown in Table 5. No correlation ($P > 0.05$) was observed between L-carnitine, chromium, ractopamine and somatotropin supplementation and the total number of piglets born. However, a positive correlation ($r = 0.666$, $P < 0.05$) was observed between total number of piglets born and L-arginine supplementation. Supplementation with L-carnitine and chromium had a positive correlation ($r = 0.401$, $P < 0.05$) with the number of piglets born alive. There was a positive correlation between birth weight of piglets and supplementation with L-carnitine, L-arginine and somatotropin ($r = 0.973$, $r = 0.565$, $r = 0.448$, respectively; $P < 0.05$). A strong positive correlation ($r = 0.985$, $P < 0.001$) was found between the number of weaned piglets and the administration of somatotropin in pregnant sows. Furthermore, the administration of somatotropin during

Table 2
Feed intake, body weight and backfat thickness of pregnant and lactating sows fed with diets supplemented with nutritional modulators or somatotropin administration.

	L-carnitine				L-arginine				Chromium				Somatotropin[1]			
	n	No	Add	rsd^{P}	*n*	No	Add	rsd^{P}	*n*	No	Add	rsd ^{P}	*n*	No	Add	rsd^{P}
ADFI G, kg/d[2]	*23*	3.17	3.33	5.89^{ns}	*113*	5.84	5.61	1.85^{ns}	*25*	4.88	5.28	2.37^{ns}	*105*	4.23	4.74	5.71^{ns}
ADFI L, kg/d[3]	*120*	5.38	5.75	3.40*	*97*	5.57	5.60	1.81^{ns}	*41*	8.13	7.90	1.70 ^{ns}	*22*	5.40	4.72	3.14^{ns}
BW IA, kg[1]	*68*	166	165	1.92^{ns}	*11*	153	140	3.32^{ns}	-	-	-	-	*42*	162	166	1.26^{ns}
BT InG, mm[2]	*32*	13.0	13.3	3.49^{ns}	*10*	14.2	14.1	0.71^{ns}	-	-	-	-	*12*	11.0	12.8	16.5^{ns}
BT FinG, mm[2]	*22*	21.5	22.3	3.21^{ns}	-	-	-	−	-	-	-	−	*7*	15.5	15.8	5.76 ^{ns}
BT Frwg, mm[3]	-	-	-	-	*16*	14.9	13.9	6.64^{ns}	-	-	-	-	-	-	-	-

n, number of treatments available in each variable; G: Gestation, L: Lactation, ADFI: average daily feed intake, BW IA: body weight of sow at insemination; BT: backfat thickness, mm (InG: initial at gestation; FinG: final at gestation; Frwg: at farrowing); No: diets without and Add: diets with nutritional modulators.
rsd: residual standard deviation, $P<0.05$: *, $P<0.01$: **, $P<0.001$: ***

^{ns} : not significant

[1] supplemented in gestation diets and evaluated in sows in lactation phase.

[2] Levels supplemented in gestation phase (minimum - maximum): L-car: 25 – 435 mg/d of L-carnitine; L-arg: 0.4 – 1.5% of L-arginine; Cr: 200 – 1000 ppm/kg diet of chromium; pST: 10 – 70 mg/d of Somatotropin.

[3] Levels supplemented in lactation phase (minimum - maximum): L-car: 25 – 350 mg/d of L-carnitine; L-arg: 0.5 – 2.0% of L-arginine;

- Dash (empty cells) indicate lack of information in the variable response.

Table 3
Pearson's correlations (r) between nutritional modulators supplemented in diets or somatotropin administration and average daily feed intake and body condition of pregnant and lactating sows.

	Dietary modulators supplemented in Gestation diets				Lactation	
	L-car, mg/d	L-arg, %	Cr, ppm/d	pST, mg/d	L-car, mg/d	L-arg, %
Variables						
ADFI, kg/d	(*123*) 0.342^{ns}	(*113*) -0.703^{ns}	(*25*) 0.665^{ns}	(*105*) -0.191^{ns}	(*120*) 0.070^{ns}	(*97*) 0.885*
SWW, kg	-	-	-	-	(*30*) -0.064 ^{ns}	(*11*) -0.097^{ns}
BT InG, mm	(*32*) 0.263^{ns}	(*10*) -0.055^{ns}	-	(*8*) -0.643^{ns}	-	-
BT FinG, mm	(*22*) 0.481^{ns}	-	-	(*12*) 0.299 ^{ns}	-	-
BT Farrowing, mm	-	(*16*) -0.509^{ns}	-	-	(*12*) 0.023^{ns}	(*25*) -0.167^{ns}
BT Weaning, mm	-	-	-	-	(*20*) 0.072 ^{ns}	-

(*n*) number of treatments available in each variable; ADFI: average daily feed intake, kg/d; SWW, kg: sow weight at weaning; SBT: sow backfat thickness, mm (InG: initial at gestation; FinG: final at gestation);
Pearson correlation (r): $P < 0.05$: *, $P < 0.01$: **, $P < 0.001$: ***
^{ns} : not significant.
[1]Levels supplemented in gestation phase (minimum - maximum): L-car: 25 – 435 mg/d of L-carnitine; L-arg: 0.4 – 1.5% of L-arginine; Cr: 200 – 1000 ppm/kg diet of chromium; pST: 10 – 70 mg/d of Somatotropin.
[2]Levels supplemented in lactation phase (minimum - maximum): L-car: 25 – 350 mg/d of L-carnitine; L-arg: 0.5 – 2.0% of L-arginine;
-Dash (empty cells) indicate lack of information in the variable response.

Table 4
Productive performance of litter from sows receiving somatotropin administration during gestation or diets supplemented with dietary modulators supplemented gestation and lactation.

	L-carnitine[3]				L-arginine[3]				Chromium[3]				Somatotropin[1,2]				Ractopamine[1,2]			
	n	No	Add	rsd^{P}	*n*	No	Add	rsd^{P}	*n*	No	Add	rsd ^{P}	*n*	No	Add	rsd^{P}	*n*	No	Add	rsd^{P}
Piglets, n																				
Total	*61*	12.01	11.95	6.29 ^{ns}	*33*	14.22	14.31	2.14 ^{ns}	*30*	11.81	11.83	0.67^{ns}	*38*	11.60	11.50	9.86 ^{ns}	*5*	-	-	-
Live	*105*	11.00	11.26	3.07 *	*23*	13.31	13.12	4.28 ^{ns}	*21*	10.05	10.55	4.71***	*49*	10.47	10.26	5.27 ^{ns}	*30*	12.24	11.65	5.50 ^{ns}
Stillborn	*38*	0.67	0.81	1.34 ^{ns}	*18*	1.65	1.24	1.29 *	*10*	1.08	1.09	8.53 ^{ns}	*19*	0.96	1.06	3.42 ^{ns}	*20*	1.77	2.54	5.82 ^{ns}
Mummified	*15*	0.55	0.39	0.19 ^{ns}	*20*	1.55	0.30	1.04 *	*7*	-	-	-	*20*	0.18	0.25	0.61 ^{ns}	*20*	3.37	3.50	4.85 ^{ns}
Weaned	*12*	8.70	9.17	0.43^{ns}	*22*	10.18	10.34	0.71 ^{ns}	*18*	7.47	7.96	8.73 ^{ns}	*15*	7.87	8.65	0.39 ***	*11*	9.70	9.49	7.99 ^{ns}
BW birth, kg	*61*	1.45	1.53	0.87 ***	*43*	1.40	1.44	2.63 **	*12*	1.40	1.45	3.79 ^{ns}	*48*	1.45	1.50	0.08 **	*25*	1.62	1.64	4.56 ^{ns}
BW weaning, kg	*6*	-	-	-	*15*	8.72	8.70	0.64 ^{ns}	*7*	-	-	-	*32*	7.55	7.87	2.95 ^{ns}	*12*	6.05	6.13	5.65 ^{ns}

(*n*) number of treatments available in each variable; Piglets, n: number; BW birth, kg: piglet body weight; BW weaning, kg: piglet body weight at weaning.
rsd: Residual standard deviation, Probability: $P < 0.05$*, $P < 0.01$**, $P < 0.001$***, ns not significant;
[1] supplemented in gestation diets and evaluated in sows in lactation phase.
[2] Levels supplemented in gestation phase (minimum - maximum): L-car: 25 – 435 mg/d of L-carnitine; L-arg: 0.4 – 1.5% of L-arginine; Cr: 200 – 1000 ppm/kg diet of chromium; pST: 10 – 70 mg/d of Somatotropin; Rac: 20 ppm/d diet of Ractopamine.
[3] Levels supplemented in lactation phase (minimum - maximum): L-car: 25 – 350 mg/d of L-carnitine; L-arg: 0.5 – 2.0% of L-arginine.
- Dash (empty cells) indicate lack of information in the variable response.

Table 5
Pearson's correlations (r) between responses on piglet's performance and lactating sows receiving diets supplemented with dietary modulators.

	Lactation[1]			Gestation[2]	
	L-car, mg/d	L-arg, %	Cr, ppm/kg	Rac, ppm/d	pST, mg/d
Variables					
Piglets, n					
Total	(*61*) 0.287^{ns}	(*33*) 0.696*	(*30*) -0.077^{ns}	-	(38) 0.027^{ns}
Live	(*105*) 0.401*	(*23*) -0.270^{ns}	(*21*) 0.552**	(*30*) -0.166^{ns}	(49) -0.053^{ns}
Stillborn	(*38*) 0.227^{ns}	(*18*) 0.369^{ns}	(*10*) 0.093^{ns}	(*20*) 0.318^{ns}	(19) 0.308^{ns}
Mummified	(*15*) -0.619^{ns}	(*20*) 0.213^{ns}	-	(*20*) 0.177^{ns}	(20) 0.450^{ns}
Weaned	-	(*22*) -0.370^{ns}	(*18*) 0.704^{ns}	(*11*) -0.130^{ns}	(15) 0.985***
BW birth, kg	(*61*) 0.973 ***	(*43*) 0.565**	(*12*) 0.065^{ns}	(*25*) 0.279^{ns}	(48) 0.448**
BW weaning, kg	-	(*15*) -0.707^{ns}	-	(*12*) 0.184^{ns}	(32) 0.067^{ns}
N° experiments	22	19	11	10	20

(*n*) number of treatments available in each variable; Piglets, n: number; BW birth, kg: piglet body weight; BW weaning, kg: piglet body weight at weaning.
Pearson correlation (r): $P < 0.05$: *, $P < 0.01$: **, $P < 0.001$: ***, ns: not significant.
[1] Levels supplemented in lactation phase (minimum - maximum): L-car: 25 - 350mg/d of L-carnitine; L-arg: 0.5 – 2.0% of L-arginine; Cr: 200 – 500 ppm/kg diet of chromium;
[2] Rac: 20 ppm/d diet of Ractopamine; pST: 10 – 70 mg/d of Somatotropin administration during gestation period;
- Dash (empty cells) indicate lack of information in the variable response.

gestation increased ($P < 0.05$) the number of piglets weaned by 9.0% compared to that of the control group.

3.4. Nutritional requirements

The relationship between nutrient levels recommended for sows, according to the Nutrient Requirements of Swine (NRC, 2012) and Brazilian Tables for Poultry and Swine (Rostagno et al., 2011), and the levels provided in the articles, is presented in Fig. 1. Only 48 of the 66 publications (73%) presented information on the nutritional composition of diets. In 29 of these 48 of publications, sows exhibited lower metabolizable energy intakes than the NRC (2012) recommendations. In the 19 remaining publications, the metabolizable energy intake was lower than the recommendations of the Brazilian tables (Rostagno et al., 2011).

In 20 of 48 publications, the total lysine consumption was higher than the recommendations of the NRC (2012). In 28 of 48 publications, it was higher than the recommendations of the Brazilian tables (Rostagno et al., 2011). The methionine provided was higher than the NRC-recommended level in 12 publications. 100% of the studies (48 of 68 publications that presented nutritional composition) showed higher intakes of methionine than those recommended by the Brazilian tables (Rostagno et al., 2011). About 50% of the publications mentioned higher intake of threonine, while the remaining had lower intakes. Similarly, tryptophan intake was lower than the NRC recommendations (2012) in 50% of publications and higher in the other 50%. Tryptophan intake was higher than the level recommended by the Brazilian tables (Rostagno et al., 2011) in all 48 publications. In our meta-analysis, the use of calcium (Ca) and phosphorus (P) was above the levels recommended by the NRC (2012) and the Brazilian tables (Rostagno et al., 2011). The studies that reported lower amounts of nutrients than those recommended by the NRC (2012) and the Brazilian tables (Rostagno et al., 2011) were considered in the analyses to determine if the lack of these essential nutrients influenced the action of nutritional modulators. We found that variation in nutrient intake from the values recommended in the nutritional tables did not influence the number and weight of piglets at birth.

4. Discussion

Some of the studies included in our meta-analysis involved small sample sizes that may not be sufficient to prove effects, as in studies evaluating L-carnitine (Birkenfeld et al., 2006) and chromium (Lindemann et al., 2004). However, one of the advantages of meta-analysis is that it increases the size of the sample population, which improves statistical power, by integrating several studies on the same theme (Sauvant et al., 2008). The magnitude of the responses of sows to nutritional modulators may be affected by geographic, genetic, and production system differences, among others (Lindemann et al., 2004). This variability between studies has great analytical weight, but is considered in the study of covariance, without prejudice to the overall analysis of the meta-analysis.

This meta-analysis shows that nutritional modulators do not affect daily feed intake, body weight nor backfat thickness of sows during pregnancy. Moreover, through this study, we identified that these variables are little explored in experiments involving nutritional modulators for pregnant and lactating sows. Feed intake directly affects the body condition of the sow, but, during pregnancy, feed intake is controlled to avoid excessive weight gain and backfat accumulation. Our results corroborate the findings of Birkenfeld et al. (2006), Bérard and Bee (2010), Gatford et al., (2010), and Garbossa et al., (2015), who found that nutritional modulators do not affect sow body performance. Among the modulators evaluated, only ractopamine can alter body composition by acting on protein and lipid synthesis (Dunshea et al., 2016). However, we did not observe any improvement in the performance of ractopamine-supplemented sows and their litters, although we found that there is a lack of information regarding the use of ractopamine in pregnant and lactating sows, possibly due to the ban on its use in pig production in many countries (Alemanno and Capodieci, 2012).

In relation to the control group, the dietary modulators resulted in better reproductive indices, including lower rates of stillbirths and mummified piglets, as well as larger numbers of total piglets born to sows fed with L-arginine. These results may be associated with better uterine condition as well as increased blood flow and placental permeability, which increase embryonic survival during pregnancy (Wu et al., 2010; Oksbjerg et al., 2013). L-arginine is responsible for the development of the placenta and porcine fetus, as it is a precursor of nitric oxide, and is responsible for the synthesis of polyamines (Wu et al., 2013). Nitric oxide acts on the vascularization of the placenta and regulates blood flow, affecting the transfer of nutrients and oxygen from the mother to the fetus. Nitric oxide and polyamines participate in angiogenesis and embryogenesis, which may explain the positive correlation between L-arginine supplementation in sows and the number of piglets born found in our meta-analysis.

Supplementing sows with both L-carnitine and chromium during gestation increased the number of live-born piglets as compared to non-supplemented sows. Both modulators act on uterine nutrients and oxygen, contributing to greater embryonic survival, fetal growth, and greater homogeneity of litters at birth. Among other characteristics, L-carnitine can alter nutrient partitioning and energy flow at placental and tissue levels, improving intrauterine nutrition, and consequently the survival of piglets (Ringseis et al., 2018). Chromium supplementation can also enhance insulin action, resulting in reduced blood insulin levels, since improved insulin action means less insulin is required to promote glucose uptake by tissues (Wray-Cahen, 2001). In this context, the highest embryonic survival and, in turn, the highest number of piglets at birth is related to ovarian development, granulosa cell proliferation, and maturation and stimulation of progesterone production through increased blood insulin (Lindemann and Lu, 2018).

Sows supplemented with L-carnitine, L-arginine, and administered somatotropin during pregnancy had piglets with higher birth weights than non-supplemented sows. This result may be associated with uterine nutritional modulation through increased nutrient availability to the fetus. The fetal growth rate is sensitive to the rates of placental delivery of nutrients and oxygen from maternal to fetal blood (Oksbjerg et al., 2013; Wang et al., 2013). Thus, modulators may directly or indirectly affect uterine environment conditions, through better nutrient supply with L-arginine (Wu et al., 2010; Oksbjerg et al., 2013), L-carnitine (Ringseis et al., 2018), and somatotropin (Gatford et al., 2010). Maternal somatotropin exerts a considerable effect on nutrient transfer through the placenta, which improves the growth conditions of piglets in the litter.

Somatotropin administration to sows during pregnancy increased the number of weaned piglets. Higher birth weights and increased availability of sow's milk may have increased the survival rate of these piglets. The increase in newborn piglet weight in sows supplemented with somatotropin may be related to the elevation of IGF-I, which acts on the proliferation and differentiation of myogenic cells, improving the growth and development of piglets (Rekiel et al., 2014). Gatford et al. (2010) suggested that somatotropin increases fetal growth via changes in maternal metabolism that increase the availability of nutrients to the fetus. However, even with optimal sow nutrition, fetal growth is not sustained when somatotropin administration ceases in mid-pregnancy (Villanueva et al., 2006).

In approximately half of the studies that provided information on nutritional composition of the diets used, the estimated metabolizable energy and ingested lysine for pregnant sows was lower than that recommended in tables by Rostagno (2011) and NRC (2012), as show in Fig. 1. In recent years, genetic improvements in sows have resulted in an increase in the speed of maternal gain, an increase in the number of piglets born, and higher milk production. Approximately 70% of the studies included in our meta-analysis used the nutritional recommendation tables published in 1988 and 1998. In relation to the NRC (2012), the recommendation tables used by the studies in this database indicate lower DE (13.5% lower, NRC, 1988) and ME (7.6% lower, NRC, 1998) requirements for pregnant sows. In this context, there was a 1.5% increase in the recommended amount of digestible lysine (g/d) between the tables from 1998 to 2012. This increase is related to maternal gain (increase of +10 kg/sow) and litter size (increase of +1.5 piglets/sow). However, this increase in requirements did not change the mean tabulated values of amino acids, but did change the supply of these amino acids in different periods during pregnancy. Currently, NRC (2012) nutritional tables recommend a higher amino acid intake after 90 days of gestation, and Rostagno et al. (2011) recommend a higher amino acid intake after 86 days of gestation. Current suboptimal feeding programs for gestating sows can compromise the amino acid availability for fetal development (Wu et al., 2010). In this context, greater availability of amino acids for sows may improve maternal and embryonic-fetal nutrition, as in the case of L-arginine (Wu et al., 2010; Dallanora et al., 2017). In this meta-analysis, we found that amino acid intake by pregnant sows was higher than that recommended by Rostagno et al. (2011) and NRC (2012). Adequate nutrient intake associated with the use of nutritional modulators during the sows' pregnancy may have positively affected reproductive performance.

The direct action of nutrients, and the indirect mechanisms mediated by nutritional modulators, can act synergistically on fetal growth (Oksbjerg et al., 2013). This growth varies according to the availability of circulating nutrients in the sow and the efficiency of nutrient transfer through the placenta to the fetus (Rekiel et al., 2014). During pregnancy, the need for Ca and P increases proportionally with fetal growth, and is also affected by milk production in the sow during lactation. However, somatotropin administration in pigs decreases daily feed intake, and adjustments in dietary Ca and P levels are required. Lower feed intake, associated with somatotropin administration, may compromise bone mineralization in gilts during early growth and development, and result in carcass leanness (NRC, 2012).

Recently, many countries have banned the use of ractopamine, somatotropin, and chromium tricopilonate supplements in pig production due to risks associated with human health. However, this study allowed us to summarize information on the use of these nutrient modulators in the diet of pregnant and lactating sows in years prior to the ban, and in countries where their use is still permitted. Furthermore, this meta-analysis allowed us to relate the different nutritional modulators and the nutritional composition of diets of pregnant and lactating sows to their impacts on body condition and reproductive performance.

5. Conclusion

Responses of sow's body condition to nutritional composition of diets are not provided uniformly in studies with nutritional modulators, which makes it impossible to reach conclusions about the efficient use of these additives for nutritional adjustments in pregnant and lactating sows. However, there is an improvement in the performance of litters of sows fed with diets supplemented with L-carnitine, L-arginine, chromium and somatotropin, during gestation and lactation.

CRediT authorship contribution statement

Lidiane Pescke Pereira: Writing - original draft, Methodology, Formal analysis. **João Otávio Hilgemberg:** Data curation, Writing - review & editing. **Anna Paula Holzmann Mass:** Writing - review & editing. **Cheila Roberta Lehnen:** Formal analysis, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Supplementary materials

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References

Alemanno, A., Capodieci, G., 2012. Testing the limits of global food governance: the case of ractopamine. Eur. J. Risk Regul. 3, 400–407. https://doi.org/10.1017/S1867299X00002294.

Bérard, J., Bee, G., 2010. Effects of dietary L-arginine supplementation to gilts during early gestation on foetal survival, growth and myofiber formation. Animal 4, 1680–1687. https://doi.org/10.1017/S1751731110000881.

Birkenfeld, C., Doberenz, J., Kluge, H., Eder, K., 2006. Effect of l-carnitine supplementation of sows on l-carnitine status, body composition and concentrations of lipids in liver and plasma of their piglets at birth and during the suckling period. Anim. Feed Sci. Technol. 129, 23–38. https://doi.org/10.1016/j.anifeedsci.2005.12.007.

Dallanora, D., Marcon, J., Walter, M.P., Biondo, N., Bernardi, M.L., Wentz, I., Bortolozzo, F.P., 2017. Effect of dietary amino acid supplementation during gestation on placental efficiency and litter birth weight in gestating gilts. Livest. Sci. 197, 30–35. https://doi.org/10.1016/j.livsci.2017.01.005.

Dunshea, F.R., D'Souza, D.N., Channon, H.A., 2016. Metabolic modifiers as performance-enhancing technologies for livestock production. Anim. Front. 6, 6–14. https://doi.org/10.2527/af.2016-0038.

Garbossa, C.A.P., Carvalho Junior, F.M., Silveira, H., Faria, P.B., Schinckel, A.P., Abreu, M.L.T., Cantarelli, V.S., 2015. Effects of ractopamine and arginine dietary supplementation for sows on growth performance and carcass quality of their progenies. J. Anim. Sci. 93, 2872–2884. https://doi.org/10.2527/jas.2014-8824.

Gatford, K.L., Grupen, C.G., Campbell, R.G., Luxford, B.J., Smits, R.J., Owens, P.C., Nottle, M.B., 2010. Reproductive responses to daily injections with porcine somatotropin before mating in gilts. J. Reprod. Dev. 56, 540–545. https://doi.org/10.1262/jrd.10-060T.

Lindemann, M.D., Carter, S.D., Chiba, L.I., Dove, C.R., LeMieux, F.M., Southern, L.L., 2004. A regional evaluation of chromium tripicolinate supplementation of diets fed to reproducing sows. J. Anim. Sci. 86, 2972–2977. https://doi.org/10.2527/2004.82102972x.

Lindemann, M.D., Lu, N., 2018. Use of Chromium as an animal feed supplement. In: Vincent, J. (Ed.), The Nutritional Biochemistry of Chromium(III), second ed. Elsevier, Amsterdam, pp. 79–128.

Lovatto, P.A., Lehnen, C.R., Andretta, I., Carvalho, A.D., Hauschild, L., 2007. Meta-análise em pesquisas científicas: enfoque em metodologias. Rev. Bras. Zootec. 36, 285–294. https://doi.org/10.1590/S1516-35982007001000026.

Martineau, G.P., Badoouard, B., 2009. Managing highly prolific sows. In: Proceedings of the London Swine Conference, pp. 14–30. https://www.ifip.asso.fr/sites/default/files/pdf-documentations/martineau2009.pdf.

Mukaka, MM., 2012. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J 24 (3), 69–71. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3576830/.

National Research Council (NRC), 1988. Nutrient Requirements of Swine, 9th ed. National Academies Press, Washington.

National Research Council (NRC), 1998. Nutrient Requirements of Swine, 10th ed. National Academies Press, Washington.

National Research Council (NRC), 2012. Nutrient Requirements of Swine, 11th ed. National Academies Press, Washington.

Oksbjerg, N., Nissen, P.M., Therkildsen, M., Møller, H.S., Larsen, L.B., Andersen, M., Young, J.F., 2013. Meat science and muscle biology symposium: in utero nutrition related to fetal development, postnatal performance, and meat quality of pork. J. Anim. Sci. 91, 1443–1453. https://doi.org/10.2527/jas.2012-5849.

Pacelle, W.2014. Banned in 160 nations, why is Ractopamine in US Pork? LiveScience, July, 26. https://www.livescience.com/47032-time-for-us-to-ban-ractopamine.html (accessed 18 August 2019).

Rekiel, A., Więcek, J., Batorska, M., Kulisiewicz, J., 2014. Effect of sow prolificacy and nutrition on pre and postnatal growth of progeny – a review. Ann. Anim. Sci. 14, 3–15. https://doi.org/10.2478/aoas-2013-0060.

Ringseis, R., Keller, J., Eder, K., 2018. Basic mechanisms of the regulation of L-carnitine status in monogastrics and efficacy of L-carnitine as a feed additive in pigs and poultry. Journal of Animal Physiology and Animal Nutrition 102 (6), 1686–1719. https://doi.org/10.1111/jpn.12959. In this issue.

Rostagno, H.S., Albino, L.F.T., Donzele, J.L., Gomes, P.C., Oliveira, R.F., Lopes, D.C., Ferreira, A.S., Barreto, S.L., Euclides, R.F., 2011. Tabelas Brasileiras Para Aves e Suínos: Composição de alimentos e Exigencias nutricionais. In: Viçosa., UFV. (Ed.), 3rd ed. .

Sauvant, D., Schmidely, P., St-Pierre, J.J., R., D.N., 2008. Meta-analyses of experimental data in animal nutrition. Animal 2, 1203–1214. https://doi.org/10.1017/S1751731108002280.

van Wettere, W.H.E.J., Pain, S.J., Hughes, P.E., 2016. Dietary ractopamine supplementation during the first lactation affects milk composition, piglet growth and sow reproductive performance. Anim. Reprod. Sci. 174, 87–92. https://doi.org/10.1016/j.anireprosci.2016.09.009.

Villanueva, D., Olmos-Hern, S.A., Mota-Rojas, D., Gonzalez-L, M., Trujillo-O, M.E., Acosta, B., Reyes, D.L., Ramirez, R., Alonso-Spi, M., 2006. Biochemical effects of recombinant porcine somatotropin on pig fetal growth and metabolism: a review. Am. J. Biochem. Biotechnol. 2, 129–137. https://doi.org/10.3844/ajbbsp.2006.129.137.

Wang, L., Shi, Z., Jia, Z., Su, B., Shi, B., Shan, A., 2013. The Effects of Dietary Supplementation with Chromium Picolinate throughout Gestation on Productive Performance, Cr Concentration, Serum Parameters, and Colostrum Composition in Sows. Biological Trace Element Research 154 (1), 55–61 In this issue.

Wray-Cahen, D., 2001. Performance-Enhancing Substances. In: Lewis, A., Southern, L.L. (Eds.), Swine Nutrition. CRC Press, Boca Raton, pp. 427–442.

Wu, G., Bazer, F.W., Burghardt, R.C., Johnson, G.A., Kim, S.W., Li, X.L., Satterfield, M.C., Spencer, T.E., 2010. Impacts of amino acid nutrition on pregnancy outcome in pigs: Mechanisms and implications for swine production. J. Anim. Sci. 88, E195–E204. https://doi.org/10.2527/jas.2009-2446.

Wu, G., Bazer, F.W., Satterfield, M.C., Li, X., Wang, X., Johnson, G.A., Burghardt, R.C., Dai, Z., Wang, J., Wu, Z., 2013. Impacts of arginine nutrition on embryonic and fetal development in mammals. Amino Acids 45, 241–256. https://doi.org/10.1007/s00726-013-1515-z.