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IGF-1 concentration patterns and their relationship with follicle development after weaning in young sows fed different pre-mating diets

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*Piglet birth weight and within-litter birth weight variation are important for piglet survival and growth. Pre-mating diets may improve IGF-1 and follicle development during the weaning-to-oestrus interval (**WEI**) and subsequent piglet birth weight. The objective of this study was to modulate IGF-1 concentration during late lactation and the WEI of young sows by using specific pre-mating diets supplemented with microfibrillated cellulose (**MF**), L-carnitine (**LC**) or L-arginine (**AR**). A further objective was to investigate the relationship between IGF-1 and subsequent follicle development and oestrus and ovulation characteristics. In total, 56 first-parity and 20 second-parity sows in three consecutive batches were used for this experiment. Sows received daily either wheat (CON) or wheat plus MF, LC or AR at one of two supplementation levels (low and high) during last week of lactation and WEI. From weaning onwards, follicle and corpus luteum (**CL**) diameters were repeatedly measured with ultrasound. Blood samples were collected during the WEI for IGF-1 and on day 21 of pregnancy for progesterone analyses, respectively. Insulin-like growth factor-1 concentration, follicle diameter, oestrus and ovulation characteristics and CL diameter were not affected by pre-mating diets. Low IGF-1 class (≤156 ng/ml, N = 22) sows had smaller follicles at weaning (3.5 v. 3.8 mm, P < 0.05) and a longer weaning-to-ovulation interval (147.2 v. 129.8 h, P < 0.05) than high IGF-1 class sows. In first-parity sows, high loin muscle depth (**LM**) loss sows (≥8%, N = 28) had lower IGF-1 concentrations at weaning (167 v. 214 ng/ml, P < 0.05) compared to low LM loss sows (<8%, N = 28). However, after weaning, IGF-1 concentrations increased and did not differ between high LM loss and low LM loss sows. In conclusion, the different supplemented compounds in pre-mating diets did not improve IGF-1 concentrations around weaning in young sows. Furthermore, high body condition loss caused lower IGF-1 concentrations at weaning, but these levels rapidly recovered after weaning and were related to follicle development and the interval from weaning to ovulation.*

Keywords: sow reproduction, IGF, metabolic state, follicular development, sow body condition

Implications

In large litters, high piglet birth weight and litter uniformity are important for newborn piglets survival and growth. Stimulating IGF-1 levels might be beneficial for subsequent fertility, as sows with high IGF-1 levels at weaning had larger follicles, and earlier studies have shown a relationship between subsequent embryo development and even piglet birth weight. However, our results implicate that negative energy balance during the lactation has a major impact on sow IGF-1 and follicle development. Thus, optimising sow body condition during the lactation might be one of the strategies for improving piglet survival and growth rate at subsequent birth.

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Introduction

Piglet birth weight is an important predictor for piglet survival during lactation and subsequent piglet growth (Baxter *et al.*, 2008). Large litters generally have a reduced average piglet birth weight and an increased within-litter birth weight variation (Wientjes *et al.*, 2012a). Modulating feeding strategies not only during gestation but also before ovulation have been recommended to increase piglet birth weight or decrease within-litter piglet birth weight variation (reviewed by Campos *et al.*, 2012; Wang *et al.*, 2017). Several studies have found relationships between pre-mating diets and subsequent piglet characteristics (i.e. litter size, birth weight and within-litter birth weight variation; van den Brand *et al.*, 2006 and 2009; Wientjes *et al.*, 2012b, 2012c and

2013a; Ferguson *et al.*, 2004 and 2007). For example, insulin-stimulating diets (e.g. with increased dextrose and lactose) fed to lactating or post-weaning sows increased piglet birth weight and decreased within-litter birth weight variation (van den Brand *et al.*, 2006 and 2009; Wientjes *et al.*, 2012b, 2012c and 2013a). It has been suggested that these pre-mating diets modulate IGF-1 before ovulation. Insulin-like growth factor-1 concentration before ovulation is known to be indirectly related to follicle and oocyte development by stimulating LH before ovulation (van den Brand *et al.*, 2001) and directly by stimulating follicle growth at the ovarian level (reviewed by Quesnel *et al.*, 2007). Sows' plasma IGF-1 concentration is closely related to follicular fluid IGF-1 concentration, which is crucial for follicle growth, steroidogenesis and maturation of oocyte, and therefore supports the direct effect of IGF-1 on follicle development (reviewed by Costermans *et al.*, 2019). The same mechanism was proposed for the positive influence of pre-mating high-fibre diets rich in sugar beet pulp on oocyte quality and litter size (Ferguson *et al.*, 2004 and 2007). Thus, pre-mating insulin- or IGF-1-stimulating diets, or both, seem to stimulate follicle and oocyte development that can subsequently affect piglet characteristics at birth.

Increased IGF-1 concentrations can be achieved not only by dextrose and lactose or fibre but also by L-arginine (**AR**) and L-carnitine (**LC**). For example, supplementation with AR in the sow diet increased IGF-1 concentration during lactation and gestation (Zhu *et al.*, 2017 – lactation; Guo *et al.*, 2017 – gestation) and higher levels of LC increased IGF-1 concentration during gestation (Musser *et al.*, 1999; Birkenfeld *et al.*, 2005; Doberenz *et al.*, 2006). Until now, the mechanisms by which AR and LC induce higher IGF-1 levels in sows are not clear. To our knowledge, the effects of AR and LC on follicle development also have not been investigated.

Microfibrillated cellulose (**MF**) is obtained through a fibrillation process of cellulose fibres and has been used as additives for food stabilizers and as functional food ingredients for human nutrition (Serpa *et al.*, 2016). Due to its high crude fibre content (57.6% in our experiment), we hypothesise that MF may affect oocyte quality and embryo survival, similar to high-fibre diets (Ferguson *et al.*, 2007). One proposed mechanism of the high-fibre diet is that the observed reduced systemic oestradiol (Arts *et al.*, 1991) stimulates gonadotropin, which is beneficial for follicle development and oocyte quality before ovulation (Ferguson *et al.*, 2007). However, MF has never been used as a feed ingredient in pigs.

Not only pre-mating IGF-1 concentrations are affected by diet but IGF-1 concentrations during and after lactation are also affected by sow metabolic state (van den Brand *et al.*, 2001; Wientjes *et al.*, 2013a), and younger sows (especially primiparous sows) have higher body condition losses during lactation because of a lower feed intake capacity (Hoving *et al.*, 2012). Consequently, the body condition losses of younger sows during lactation are a major factor that affects follicle development after weaning (Quesnel *et al.*, 1998; Costermans *et al.*, 2019).

Thus, the aim of this study was to evaluate the effects of different types of pre-mating diets on IGF-1 concentrations, follicle development before ovulation and subsequent reproductive performance in young sows. In addition, we investigated how these IGF-1 concentration changes during the weaning-to-oestrus interval (**WEI**) are related to body condition loss during lactation and to subsequent reproductive performance. We hypothesised that IGF-1 concentration during the WEI affects sow metabolic state and might be modulated by specific pre-mating diet additives.

Material and methods

Animals and management

This experiment was conducted in 2018 on a research herd in western Finland. First-parity ($N = 56$) and second-parity ($N = 20$) sows (DanAvl, alternate cross between Landrace (L) and Yorkshire (Y), either YLY or LYL) were used in three consecutive batches ($N = 23$, $N = 30$ and $N = 23$, respectively).

One week prior to parturition, sows were transferred to the farrowing and lactation unit where they were housed in individual farrowing crates. Within 2 days after farrowing, litters were standardised to 13 or 14 piglets. The average litter size at 1 week before weaning was 13.2 ± 1.0 and at weaning 11.9 ± 1.0. After weaning at 26.1 ± 0.2 day of lactation, the sows were moved into the insemination units with individual stalls. From weaning onward, oestrus detection was performed daily at 1200 h by a farm technician using fence-line boar contact. Sows were artificially inseminated once on every day of oestrus with a commercial dose of semen (mostly for two consecutive days; 2×10^9 sperm cells; DanAvl; Finnpig, Finland). Pregnancy check with ultrasound was performed by a farmer 35 days after the first insemination.

Feeding

In the farrowing and lactation unit, sows were fed liquid feed (1:3.35, feed to water ratio) four times a day and water *ad libitum*. Before farrowing and in the first 2 weeks of lactation, sows received a standard commercial lactation diet (9.2 MJ net energy (NE)/kg DM, 13.8% CP, 4.4% crude fat, 6.7% crude fibre and 0.8% lysine; Imetys Pekoni 1; Hankkija Oy, Finland). After 2 weeks of lactation, sows received another lactation diet until weaning (9.9 MJ NE/kg DM, 15.3% CP, 5.2% crude fat, 4.3% crude fibre and 1.0% lysine; Imetys Pekoni 2; Hankkija Oy, Hyvinkää, Finland). The dry feed allowance before farrowing was 2.99 kg/day and gradually increased to 7.45 kg/day during the first 2 weeks of lactation. After the first 2 weeks of lactation, the maximum feed allowance was 7.45 kg/day. From weaning until oestrus, sows were fed 4.6 kg/day of a commercial gestation diet twice a day (0700 h and 2000 h). From day 0 of gestation (day of the first insemination) to day 35 of gestation, sows were fed 3.37 kg/day of commercial gestation diet. The gestation diet was formulated to contain 9.0 MJ NE/kg DM, 11.5% CP,

4.0% crude fat, 4.0% crude fibre and 0.6% of lysine (Tiineys Pekoni 1; Hankkija Oy, Hyvinkää, Finland).

Dietary treatments

Sows were assigned to one of seven dietary treatments given during the last week of lactation (period 1) and the WEI (period 2). Allocation to treatments was stratified based on parity, BW loss (kg) between 1 day after farrowing and allocation and number of piglets at allocation. During treatment periods, sows received once daily a top dressing of 200 g, consisting of either wheat (CON) or wheat plus MF (Betulium® Microfibrillated cellulose, Espoo, Finland), L-carnitine (LC; Carniking™, Lonza Group, Inc., Allendale, NJ, USA) or L-arginine (AR; L-arginine, Cheiljedang, Indonesia) at one of two supplementation levels (see Tables 1 and 2). The top-dressed diets were analysed for DM (EU 152/2009), CP (Dumas methods), crude fat (EU 98/64), crude fibre (EU 92/89) and ash (EU 152/2009).

Bodyweight, backfat and loin muscle depth

Sow BW, backfat thickness (**BF**) and loin muscle depth (**LM**) were measured 1 day after farrowing, 1 week before weaning and at weaning. Backfat thickness and LM were measured at P2 on the right and left side of the sow (at 6 cm from the midline straight above the last rib bone) using a B-mode ultrasound with a 10.0 MHz linear array probe (MyLab One VET; Esaote, The Netherlands). Backfat thickness was measured as the length between the skin and muscle layer and LM was measured as the length between the fat layer and rib bone. Backfat thickness and LM were measured at two different points within each ultrasound image and averaged.

Follicle development, oestrus and ovulation

Trans-rectal ultrasonography with an 8-MHz linear array probe (MyLab One VET; Esaote, The Netherlands) was performed to assess follicle diameter on the day of weaning, 3 days after weaning and at 12 h intervals during oestrus

Table 1 *Composition of the experimental top-dressed diet of sows during period 1 (1 week before weaning)*

Ingredients	CON	MF1	MF2	LC1	LC2	AR1	AR2
Wheat (g)	200.0	192.5	185.0	199.75	199.62	125.5	88.2
Microfibrillated cellulose (g)	–	7.5	15.0	–	–	–	–
L-carnitine (g)	–	–	–	0.25	0.38	–	–
L-arginine (g)	–	–	–	–	–	74.5	111.8
Total (g)	200.0	200.0	200.0	200.0	200.0	200.0	200.0
Calculated value							
Energy (NE MJ/kg DM)	2.5	2.4	2.3	2.5	2.5	2.8	2.9
Analysed value (%)							
DM	89.9	89.5	89.7	89.1	89.2	92.7	94.4
CP	16.8	16.2	15.6	16.8	16.9	77.4	93.9
Crude fat	5.4	5.5	5.4	5.7	5.6	3.3	2.7
Crude fibre	7.7	9.2	11.6	7.7	7.5	5.3	3.8
Crude ash	4.4	4.5	4.7	4.3	4.4	2.8	2.1

NE = net energy.

Table 2 *Composition of the experimental top-dressed diet of sows during period 2 (from weaning to first oestrus)*

Ingredients	CON	MF1	MF2	LC1	LC2	AR1	AR2
Wheat (g)	200.0	195.4	190.8	199.77	199.65	153.8	130.7
Microfibrillated cellulose (g)	–	4.6	9.2	–	–	–	–
L-carnitine (g)	–	–	–	0.23	0.35	–	–
L-arginine (g)	–	–	–	–	–	46.2	69.3
Total (g)	200.0	200.0	200.0	200.0	200.0	200.0	200.0
Calculated value							
Energy (NE MJ/kg DM)	2.5	2.4	2.4	2.5	2.5	2.7	2.8
Analysed value (%)							
DM	89.9	89.5	89.7	89.4	89.3	91.6	92.6
CP	16.8	16.0	16.0	16.2	16.2	56.9	75.5
Crude fat	5.4	5.1	5.1	5.3	5.2	4.0	3.3
Crude fibre	7.7	8.9	10.4	7.6	8.5	6.5	5.0
Crude ash	4.4	4.4	4.4	4.2	4.5	3.4	2.8

NE = net energy.

until ovulation. The time of ovulation was defined as 6 h before the first scan when no pre-ovulatory follicles were found. The oestrus rate was calculated as the percentage of sows that showed oestrus within day 8 after weaning. In addition, ultrasonography was performed on day 21 of pregnancy to assess the diameter of the corpus luteum (**CL**). Ultrasound clips were taken from one ovary only due to bilaterally synchronised ovarian function in sows (Soede N. M., unpublished results). The clips were exported in DICOM format and analysed using the DICOM viewer Horos (Version 3.3.2, available at www.horosproject.org). Follicle diameter was determined as the mean of the five largest follicles. Follicle diameter at ovulation was defined as the largest measured follicle diameter during oestrus. Luteal diameter was determined as the mean of the five largest CL.

Blood sampling

Blood samples for IGF-1 were taken from the *vena coccygea* 30 min before feeding at 1 week before weaning, weaning, 3 days after weaning and the second day of oestrus. The samples were collected into 3-ml EDTA tubes (VACUETTE® K2EDT, Greiner Bio-One Italia, Cassina de Pecchi, Italy), immediately placed on ice and centrifuged at 1710×**g** for 10 min at 4°C. Blood samples for progesterone were taken from the *vena coccygea* on day 21 of pregnancy. The samples were collected into 4-ml heparin tubes (VACUETTE® TUBE, Greiner Bio-One Italia, Cassina de Pecchi, Italy) and immediately centrifugated at 3000×**g** for 15 min. Plasma was stored at −20°C until analyses.

Plasma analyses

Sensitivity and intra- and inter-assay coefficients of variation for IGF-1 and progesterone were presented in Supplementary Material S1.

IGF-1. IGF-1 concentrations were analysed using a commercial kit (IRMA IGF-1 A15729®; Immunotech, Marseille, France) after extraction of the samples with ethanol and HCl (as validated by Louveau and Bonneau, 1996).

Progesterone. Progesterone concentrations were analysed using a commercial radioimmunoassay (RIA; ImmuChem™ Coated Tube ^{125}I Progesterone KIT, MP Biomedicals, CA, USA) validated to measure progesterone in pig plasma.

Statistical analyses

In total, 13 sows (1 AR1, 2 AR2, 4 CON, 2 LC1, 2 LC2, 1 MF1 and 1 of MF2) did not show oestrus and were excluded from analyses on WOI, oestrus duration and follicle diameter at ovulation. One sow (AR2) showed oestrus but was not inseminated because of lameness and four sows (1 CON, 1 MF1 and 2 of AR1) inseminated after weaning were not pregnant 35 days after the first insemination. Thus, these five sows were excluded from analyses on luteal development at 21 days after the first insemination.

SAS 9.4 (SAS Inst. Inc., Cary, NC, USA) was used for statistical analyses of all data (Supplementary Material S2). Normality of the parameters was checked with the UNIVARIATE procedure using the Shapiro–Wilk test. The normally distributed parameters (IGF-1 concentrations, follicle and CL diameter) were analysed with the MIXED procedure (model 1). Non-normally distributed parameters (weaning-to-ovulation interval (WOI), oestrus duration, oestrus and pregnancy rate and progesterone concentrations) were analysed with the GLIMMIX procedure (model 2). Normally distributed parameters were presented as least square mean, and non-normally distributed parameters were presented as means.

Preliminary analyses showed that batches (1, 2 and 3) and breeds (YLY and LYL) were never significant and thus were used as a random effect to account for possible environmental and genetic variation in both models 1 and 2. Tukey–Kramer corrections were used for multiple comparisons.

Repeated measure was used in model 1 to assess effects of treatment (CON, MF1. MF2, LC1, LC2, AR1, AR2) and parity (1, 2) and their interaction on IGF-1 concentrations at weaning, 3 days after weaning and the second day of oestrus. In these models, IGF-1 concentration at 1 week before weaning was added as a covariate to account for pre-treatment differences.

To investigate treatment effects on follicle and luteal development, model 1 included treatment (CON, MF1. MF2, LC1, LC2, AR1, AR2), parity (1, 2) and their interactions as fixed effect. To determine whether lactation characteristics (IGF-1 concentrations before weaning, %BW loss, %BF loss or %LM loss) interacted with the treatment effect, a lactation characteristic and the interaction between the lactation characteristic and treatment were added as a covariate. The covariates and interactions were stepwise omitted from the model if they were not significant ($P > 0.05$; except for treatment, parity and their interaction).

To assess treatment effects on reproduction characteristics (i.e. WOI, oestrus duration, oestrus and pregnancy rate and progesterone concentrations), model 2 included treatment (CON, MF1. MF2, LC1, LC2, AR1, AR2), parity (1, 2) and their interactions were included as fixed effect. For WOI and oestrus duration, a gamma distribution with a log link function was fitted to model 2. For oestrus and pregnancy rate, a binomial distribution with a logit link function was fitted to model 2. For progesterone concentrations, a gamma distribution with a log function was fitted to model 2.

Retrospectively, based on IGF-1 concentrations at weaning, sows were divided in the 30% lowest IGF-1 (low-IGF1; ≤156 ng/ml), 40% average IGF-1 (middle-IGF1; 157 to 250 ng/ml) and 30% highest class (migh-IGF1; ≥251 ng/ml). Insulin-like growth factor-1 at weaning class, parity class and their interaction as fixed effects were fitted to models 1 and 2 to assess their relationship with oestrus and ovulation characteristics, follicle and luteal development and pregnancy rate.

To assess the effect of LM loss on IGF-1 concentrations, repeated measure was used in model 1 to assess the effects of body condition changes during lactation classes (high LM = loin muscle depth loss during lactation ≥8%, $N = 39$;

low LM = loin muscle depth loss during lactation <8%, $N = 37$), parity and their interaction on IGF-1 concentrations at weaning, 3 days after weaning and oestrus. Insulin-like growth factor-1 concentrations at the start of the treatment were used as a covariate.

Pearson and Spearman correlations were used for assessing relationships among normally distributed and non-normally distributed parameters, respectively. Relations between IGF-1 concentrations and follicular and metabolic parameters were estimated using the model: $Y_{ij} = \mu + PAR + \beta X_{ij} + \beta X \times PAR + \epsilon_{ij}$, where Y_{ij} is either one of the IGF-1 or follicular parameters, β the regression coefficient and X_{ij} is either one of the IGF-1 or metabolic parameters. The interactions were excluded from models when not significant.

Results

Feed intake and body condition loss

An overview of average daily feed intake and body condition loss of experimental sows is presented in Supplementary Material Table S1. During the lactation, sows fed on average 4.8 ± 0.7 kg and lost on average 27.2 ± 2.0 kg (12.1 ± 0.9%) of BW. Backfat thickness and LM loss during the lactation were 3.1 ± 0.2 mm (21.7 ± 1.4%) and 4.0 ± 0.7 (7.4 ± 1.2%), respectively. No differences existed in these parameters between treatment and parity. Average daily feed intake and body condition losses from starting treatment to weaning did not differ between treatment and parity (Supplementary Material Table S1).

Effect of treatment and parity on IGF-1

Pre-treatment plasma IGF-1 concentrations (1 week before weaning) tended to be higher in first-parity sows compared to second-parity sows (292 *v.* 251 ng/ml, $P = 0.07$). Insulin-like growth factor-1 concentrations between weaning and oestrus that were corrected for pre-treatment IGF-1 concentrations were not affected by treatment or by parity (Figure 1a and b). Insulin-like growth factor-1 concentrations were lowest at weaning and thereafter increased (199 *v.* 265 *v.* 265 ng/ml, respectively, $P < 0.001$). Within parity, IGF-1 concentrations at 1 week before weaning, at weaning, at 3 days after weaning and at oestrus were positively correlated to each other ($r \geq 0.50$, $P \leq 0.001$). No interactions between treatment and parity were found ($P > 0.05$).

Effect of treatment and parity on reproductive performance

Oestrus and ovarian characteristics were not affected by treatment or the interaction between treatment and parity (Table 3). Second-parity sows tended to have a larger follicle diameter during the WOI compared to first-parity sows ($P \leq 0.10$ for all; Table 3).

Relationship between IGF-1 and reproductive performance

Insulin-like growth factor-1 concentrations varied from 60 to 311 ng/ml at weaning. Within parity, this range in IGF-1 concentration was accompanied by a 0.5 mm difference in follicle diameter at weaning ($\beta = 0.002$, $P < 0.0001$; Figure 2) and also at 3 days after weaning ($\beta = 0.002$, $P = 0.06$). No significant interactions with parity were observed ($P > 0.05$).

Low-IGF1 sows had a smaller follicle diameter at weaning compared to middle- and high-IGF1 sows (3.5 *v.* 3.8 *v.* 3.8 mm, respectively, $P = 0.02$; Table 4). Low-IGF1 sows also had a longer WOI compared to high-IGF1 sows but similar compared to middle-IGF1 sows (147.2 *v.* 134.9 *v.* 129.8 h, respectively for low-, middle- and high-IGF1, $P = 0.01$).

Relationship between body condition loss and IGF-1

The percentage of BW loss, BF loss and LM loss were negatively correlated to IGF-1 at weaning ($\beta = -3$, -2 and -2 (ng/m)/%, for BW loss, BF loss and LM loss, respectively; $P < 0.01$ for all). However, no relationships were found between body condition loss and IGF-1 levels at 3 days after weaning or at oestrus. First-parity sows with high LM loss had lower IGF-1 concentrations at weaning (167 ± 13 ng/ml) than other sows (first-parity sows with low LM loss, 214 ± 13 ng/ml; second-parity sows with high LM loss,

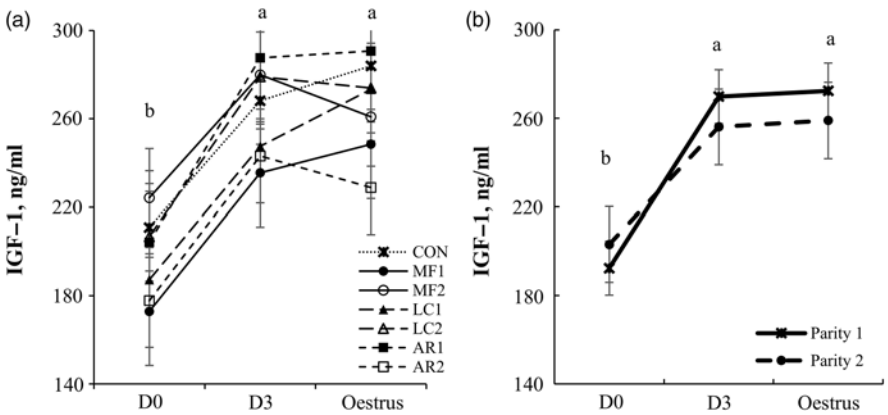

Figure 1 IGF-1 profiles (ng/ml) during the weaning-to-oestrus interval corrected for pre-treatment IGF-1 concentrations in first-parity and second-parity sows on different dietary treatments started 1 week before weaning. (a) Effect of diet; sows were fed a top-dressed diet (200 g) with either wheat (CON) or wheat and two different supplementation levels of microfibrillated cellulose (MF), L-carnitine (LC) or L-arginine (AR) and (b) effect of parity. D0 = at weaning, D3 = at 3 days after weaning; [a,b]days with different superscript differ, $P \leq 0.05$; no interactions between treatment and parity were found.

Table 3 *Oestrus and ovulation characteristics and follicle and luteal development of first-parity and second-parity sows receiving a top dressing (200 g) of either wheat (CON) or wheat plus microfibrillated cellulose (MF), L-carnitine (LC) or L-arginine (AR) at one of two supplementation levels (1,2) during 1 week before weaning and the weaning-to-oestrus interval*

	TRT								PAR			*P*-values[1]	
Items	CON ($N=10$)	MF1 ($N=10$)	MF2 ($N=12$)	LC1 ($N=10$)	LC2 ($N=12$)	AR1 ($N=11$)	AR2 ($N=11$)	RMSE	1 ($N=56$)	2 ($N=20$)	RMSE	TRT	PAR
Oestrus and ovulation													
Oestrus rate ≤7 days (%)	60.0	90.0	91.7	80.0	83.3	90.9	81.8		80.4	90.0		0.45	0.24
Weaning-to-ovulation interval (h)[2]	140.8	138.5	137.1	145.0	134.9	140.4	133.0	3.1	140.6	136.3	3.5	0.84	0.39
Oestrus duration (h)[2]	48.2	51.5	50.4	48.5	45.9	50.9	50.9	2.5	48.3	50.6	1.6	0.50	0.21
Follicle diameter (mm)													
at weaning	3.7	3.6	3.8	3.6	3.7	3.7	3.8	0.1	3.6	3.8	0.1	0.55	0.07
at 3 days after weaning	6.3	6.3	6.3	6.0	6.1	6.2	6.1	0.2	6.0	6.4	0.2	0.92	0.08
at ovulation	7.2	7.3	7.0	6.8	6.9	7.0	7.2	0.2	6.9	7.2	0.1	0.38	0.08
Luteal development													
Pregnancy rate at day 35 (%)	83.3	88.9	100	100	100	80.0	88.9		93.3	88.9		0.58	0.82
CL diameter at day 21 (mm)[3]	10.3	9.9	9.9	10.1	10.0	9.8	10.3	0.2	9.9	10.1	0.1	0.61	0.11
Progesterone at day 21 (ng/ml)[2,3]	24.5	22.6	29.4	27.3	26.5	26.2	27.0	2.4	26.1	26.2	1.4	0.74	0.97

RMSE = root mean square error; TRT = treatment; PAR = parity.
All data were presented as least square (LS) means, unless otherwise stated.
[1]The interactions between treatment and parity were not significant ($P > 0.05$) and are therefore not presented.
[2]Data were presented as means.
[3]Only pregnant sows.

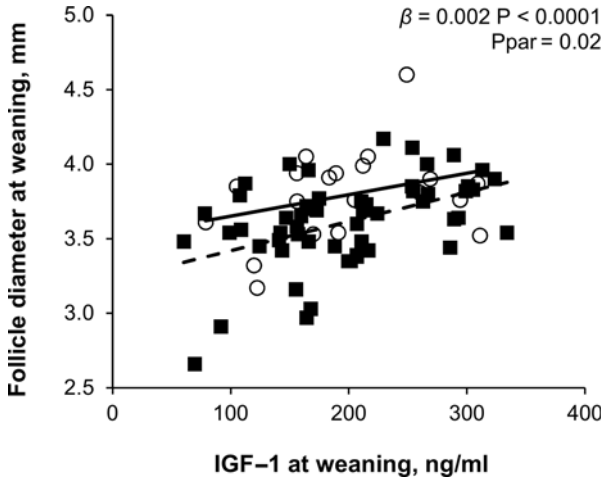

Figure 2 Relationship between IGF-1 concentrations at weaning and follicle diameter of the five largest follicles at weaning in first- (■) and second-parity sows (○). No interactions with parity were observed.

225 ± 23 ng/ml second-parity sows with low LM loss, 221 ± 16 ng/ml; $P < 0.05$; Figure 3). Lactation LM loss was not related to IGF-1 levels at 3 days after weaning or at oestrus (Figure 3).

Discussion

Top-dressed diet (MF, LC or AR) in our study did not affect average daily feed intake and sow body condition losses in late lactation. Similarly, other studies reported that LC and AR supplementation during lactation had no detrimental impact on sows' feed intake and body condition losses (Birkenfeld *et al.*, 2005; Zhu *et al.*, 2017). Thus, it seems that the inclusion level of MF, LC and AR of our study might have no detrimental impact during late lactation in sows.

Although LC and AR are known to improve sows IGF-1 after feeding, we did not find any improvement during the WEI. Wientjes *et al.* (2013a) showed that the application of IGF-1-stimulating diets only during the WEI was too short to modulate IGF-1. Therefore, our pre-mating diet supplementation started 1 week before weaning and continued during the WEI. Nevertheless, even when starting 1 week before weaning, the modulation of IGF-1 during the WEI still seems limited. This might be because the sow's negative energy balance (**NEB**) plays a major role in IGF-1 during late lactation and the WEI (will be discussed below). Furthermore, the follicle development is already ongoing during late lactation (reviewed by Britt *et al.* 1985), and the IGF-1 concentration during the WEI is positively related to IGF-1 concentration before weaning (van den Brand *et al.*, 2001; Wientjes *et al.*, 2013a; our study). Thus, IGF-1-stimulating diet during a longer period of lactation might be worth considering.

We hypothesised that specific dietary supplementations could improve IGF-1 concentrations before ovulation (i.e. preceding lactation and during the WEI) and thereby result in better developed pre-ovulatory follicles at ovulation. In earlier studies (Wientjes *et al.*, 2012a and 2013a), supplementing diets only during the WEI had no impact on IGF-1

Table 4 *Follicle development, oestrus and ovulation characteristics and luteal development in first-parity and second-parity sows (PAR; 1 (N = 56) v. 2 (N = 20)) with low (≤156 ng/ml (N = 22)), middle (157 to 250 ng/ml (N = 32)) and high (≥251 ng/ml (N = 22)) IGF-1 concentrations at weaning (IGF1)*

	IGF1				PAR			*P*-values[1]	
Items	Low	Middle	High	RMSE	1	2	RMSE	IGF1	PAR
IGF-1 (ng/ml)									
at weaning	127[c]	195[b]	281[a]	7.0	197	205	5.1	<0.001	0.29
at 3 days after weaning	208[b]	272[a]	307[a]	12.0	274	251	10.6	<0.001	0.07
at oestrus	208[b]	272[a]	308[a]	12.8	275	250	12.2	<0.001	0.11
Oestrus and ovulation									
Oestrus rate ≤ 7 days (%)	86.4	84.4	77.3		80.4	90.0		0.73	0.40
Weaning-to-ovulation interval (h)[2]	147.2[a]	134.9[ab]	129.8[b]	5.2	141.4	132.9	4.7	0.01	0.08
Oestrus duration (h)[2]	48.8	49.5	51.0	1.9	48.6	51.0	1.6	0.70	0.21
Follicle diameter (mm)									
at weaning	3.5[b]	3.8[a]	3.8[a]	0.1	3.6[y]	3.8[x]	0.1	0.02	0.04
at 3 days after weaning	6.0	6.2	6.5	0.2	6.0	6.4	0.2	0.26	0.06
at ovulation	7.0	7.0	7.1	0.2	6.9[y]	7.2[x]	0.2	0.60	<0.01
Luteal development									
Pregnancy rate at day 35 (%)	100	92.6	82.4		93.3	88.9		0.26	0.95
CL diameter day 21 (mm)[3]	10.2	9.9	10.1	0.2	9.8[y]	10.3[x]	0.2	0.32	0.03
Progesterone day 21 (ng/ml)[2,3]	27.9	25.4	25.4	2.0	26.5	25.9	1.6	0.59	0.80

RMSE = root mean square error; PAR = parity.
All data were presented as least square (LS) means, unless otherwise stated.
[a,b,c]Means within a row without a common superscript are different (IGF1 effect; $P \leq 0.05$).
[x,y]Means within a row without a common superscript are different (PAR effect; $P \leq 0.05$).
[1]The interactions between treatment and parity were not significant ($P > 0.05$) and therefore are not presented.
[2]Data were presented as means.
[3]Only pregnant sows.

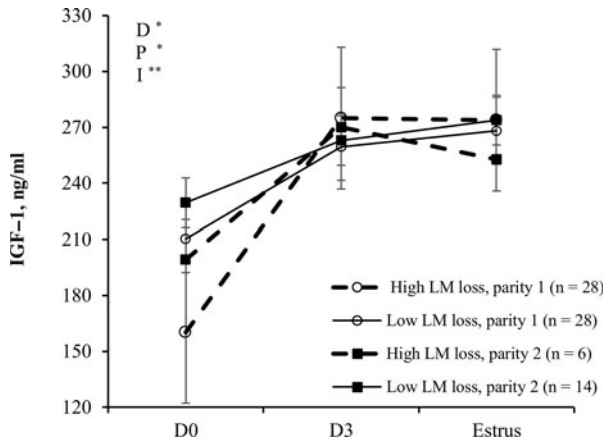

Figure 3 Effects of parity and high and low loin muscle depth (LM) loss during lactation on plasma treatment corrected plasma IGF-1 concentrations during the weaning-to-oestrus interval (WEI) in sows. D0 = at weaning; D3 = at 3 days after weaning, high LM loss = loin muscle depth loss during lactation ≥8%; low LM loss = loin muscle depth loss during lactation <8%; day effect (D); D0 differs from D3 and oestrus; $P \leq 0.05$; Parity effect (P); $P \leq 0.05$, interaction (I) between parity and loin muscle depth loss during lactation; $P \leq 0.01$.

concentration; a prolonged supplementation period also considering (late) lactation was recommended. Thus, we applied the dietary treatments during WEI and in late lactation and expected increased IGF-1 already at weaning. Nevertheless, IGF-1 concentrations were not affected by the treatments; no effect was observed at weaning or in the post-weaning period up to oestrus. The lack of effect might be related to the NEB of the sows during lactation and the sows' rapid recovery of IGF-1 after weaning (van den Brand *et al.*, 2001; Mejia-Guadarrama *et al.*, 2002; Wientjes *et al.*, 2013a). During the NEB, IGF-1 concentrations decreased because the somatotropic axis becomes uncoupled (reviewed by Lucy 2008). This uncoupling of the somatotropic axis causes lower IGF-1 and higher growth hormone concentrations in blood. However, after weaning, sows change towards an anabolic state, which involves rapid restoration of plasma IGF-1 concentrations (van den Brand *et al.*, 2001; Mejia-Guadarrama *et al.*, 2002; Wientjes *et al.*, 2012b and 2012c). The sows in this study also had a rapid recovery of IGF-1 levels within 3 days after weaning (on average +71 ng/ml, from weaning to day 3), and no relationships between body condition losses and IGF-1 concentration were observed after weaning.

Similar to previous studies that used insulin-stimulating diets to modify IGF-1 levels (Wientjes *et al.*, 2013a), our pre-mating diets did not affect follicle development, oestrus duration or WOI. However, we observed that IGF-1 concentration was positively related with follicle development during the WEI, similar to previous findings. For example, Quesnel *et al.* (2007) reported that IGF-1 before weaning was positively related to follicle size at weaning. Van den Brand *et al.* (2001) also found that follicle diameter at day 2 after weaning positively correlated with IGF-1 concentration 1 day before weaning. In the study of van den Brand *et al.* (2001), lower IGF-1 at

weaning resulted in less frequent LH pulses and a smaller surge level at weaning. Thus, we can speculate that lower IGF-1 at weaning might cause suppressed LH secretion and further impaired follicular growth in sows (reviewed by Zak *et al.*, 1997).

Besides follicular development, lower IGF-1 concentration at weaning was related to the longer WOI. Wientjes *et al.* (2013a) also reported a negative relationship between pre-weaning IGF-1 concentration and WEI ($\beta = -0.16$ h/ng per ml; $P < 0.01$). This might be because sows with lower IGF-1 concentration at weaning also have smaller follicles at weaning, and these small follicles need more time to become pre-ovulatory follicles (Langendijk *et al.*, 2000). Bracken *et al.* (2003) proposed that sows with long WOI may have less healthy follicles and thus lead to lower conception rate and litter size. Thus, we can speculate that lower IGF-1 concentration at weaning might be related to poor subsequent fertility.

Although IGF-1 levels in this study did not appear to be influenced by the dietary treatments, they were affected by lactational body condition losses, specifically LM losses. First-parity sows with high LM loss had lower IGF-1 levels at weaning compared to sows with low LM loss (167 *v.* 214 ng/ml). This is consistent with previous findings that there was a negative relationship between LM loss during lactation and IGF-1 levels at weaning, whereas BF loss did not (Hoving *et al.*, 2012). This may be the reason why LM loss had more impact on IGF-1 concentration at weaning than BF loss. However, there was a rapid restoration of IGF-1 secretion after weaning regardless of LM loss during lactation. This implies that these young sows have an ability to restore their metabolic status, as previously reported by Mejia-Guadarrama *et al.* (2002).

Nevertheless, we did find that BF and LM losses during lactation were negatively correlated to follicle diameter at weaning (data not shown). Follicle and oocyte development is important for subsequent embryo survival and development (Pope *et al.*, 1990; Zak *et al.*, 1997) and also for luteal development (Wientjes *et al.*, 2012c). Compromised follicle development can result in a pre-ovulatory follicle pool with large size variation and therefore variations in embryo development (Pope *et al.*, 1990; Zak *et al.*, 1997), which is a factor that affects birth weight variation (van der Lende *et al.*, 1990). Lower average piglet birth weights and larger within-litter birth weight variation have been seen in sows with severe body condition loss during lactation (Wientjes *et al.*, 2013b), which might result from compromised follicle development at weaning. Considering that lower IGF-1 concentration may result in compromised follicle development, sow management preventing high LM loss may be recommended for preventing lower IGF-1 concentration at weaning and subsequent reproductive consequences.

This study shows that supplementations to the pre-mating diet, consisting of L-carnitine, L-arginine, or MF, did not affect IGF-1 concentration during the WEI of young sows. Sows with higher IGF-1 concentrations at weaning, however, had larger follicles at weaning and a shorter WOI than sows with lower IGF-1 levels at weaning. High lactation weight (specifically LM) losses seem to negatively affect sow IGF-1 concentration at weaning. However, a rapid post-weaning restoration of IGF-1 concentration is seen in all sows, and the consequences of lower IGF-1 levels at weaning for subsequent fertility require further study.

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Declaration of interest

The authors declare that there are no conflicts of interest.

Ethics statement

Experimental procedures were reviewed and approved by the Animal Experiment Board (ELLA; ESAVI/2325/04.10.07/2017) in Finland.

Software and data repository resources

None of the data were deposited in an official repository.

Supplementary material

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