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Original Research Article

Lactation body condition loss impaired conceptus development and plasma progesterone concentration at day 8 post-ovulation in primiparous sows

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ABSTRACT

The current study investigated effects of dietary amino acid (AA) availability on lactational body condition loss and metabolic status, in relation to reproductive parameters after weaning up to Day 8 post-ovulation. Primiparous sows (n = 35) were allocated to one of two lactation diets containing either low crude protein (CP, 140 g/kg) with a low percentage (8%) of slow protein in total protein (LL, n = 18) or high CP (180 g/kg) with a high (16%) percentage of slow protein (HH, n = 17). The HH diet was expected to improve AA utilization by supplying more AA, in a more gradual fashion. The diets did not affect sow body condition loss during lactation, while the HH diet tended to increase litter weight gain during the week 3 of lactation ($\Delta = 1.3$ kg, $P = 0.09$). On Day 14 post-farrowing, HH diet led to higher plasma urea both pre-feeding and post-feeding ($\Delta = 2.3$ mmol/L, $P < 0.01$, $\Delta = 2.4$ mmol/L, $P < 0.01$, respectively), whilst plasma creatinine, NEFA and IGF-1 were similar. No dietary effects on reproductive parameters were found, however several relationships were found between body condition and reproductive parameters. Sows with higher body weight on Day 1 or Day 21 post-farrowing had greater follicle size on Day 3 post-weaning ($\beta = 0.03$ mm/kg, $P < 0.01$, $\beta = 0.04$ mm/kg, $P < 0.01$, respectively). At Day 8 post-ovulation, plasma progesterone concentration was negatively related to loin muscle loss ($\beta = -0.67$ ng/ml · mm^{-1}, $P = 0.02$), backfat loss ($\beta = -2.33$ ng/ml · mm^{-1}, $P = 0.02$), and estimated body fat loss ($\beta = -0.67$ ng/ml · mm^{-1}, $P = 0.02$). Both plasma progesterone and the number of corpora lutea were positively related to the energy balance during lactation ($\beta = 0.03$ ng/ml · ME MJ^{-1}, $P = 0.01$, $\beta = 0.01$ CL/ME MJ, $P = 0.02$, respectively). The conceptus size at Day 8 post-ovulation was negatively related to body weight loss ($\beta = -0.01$ mm/kg, $P = 0.01$), estimated body fat loss ($\beta = -0.02$ mm/kg, $P = 0.03$) and estimated body protein loss ($\beta = -0.06$ mm/kg, $P = 0.04$), and was positively related to the energy balance during lactation ($\beta = 5.2*10^{-4}$ mm/ME MJ, $P = 0.01$). In conclusion, body protein and fat losses during lactation reduced subsequent plasma progesterone concentration and conceptus development at Day 8 post-ovulation.

1. Introduction

Modern hybrid sows often mobilize body tissue to sustain high milk production for their large litters [1]. This applies particularly to primiparous sows, since their voluntary feed intake is lower than multiparous sows [2]. A high body condition loss during lactation can negatively affect subsequent reproductive performance, including prolonged weaning-to-oestrus interval, lower farrowing rate, reduced litter size [3–5], and increased within-litter variation in birth weight [6]. The compromised performance of the next litter could be associated with changes in reproduction-associated hormones, and/or impairment of follicular and oocyte development. For instance, sows that lost more body weight had lower follicular fluid insulin-like growth factor-1 (IGF-1) at Day 2 post-weaning [7]. A changed follicular development affects not only oocyte development and thereby embryo development [8], but also the development of the corpora lutea (CL) and progesterone (P4) secretion (reviewed in Ref. [9]). Sows with higher lactational weight loss had lower P4 concentrations during Day 4 to Day 16 of gestation [10], while P4 plays an indispensable role in the subsequent embryo growth (reviewed in Ref. [11]). Consequently, impaired embryo

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survival, growth, and uniformity will influence litter size, piglet birth weight and within-litter variation in birth weight at the next farrowing [6,12,13].

With modern sows developing into a leaner genotype that has less fat reserves, body protein mobilization has even more severe effects on reproductive performance than fat tissue loss [4,7]. Hence, improving the availability of dietary amino acid (AA) for milk synthesis is critical to minimise sow body protein tissue mobilisation during lactation. Previous studies showed that feeding a higher total crude protein (CP) could spare body protein and sustain milk production [3,14,15]. In addition, the digestion kinetics of dietary protein has appeared to be another crucial factor affecting dietary AA availability, and thereby sow and litter performance during lactation. In our previous study, feeding a higher concentration of protein degraded at a slower rate (degrading between 30 and 240 min in vitro), in contrast to protein degraded at a fast rate (degrading within 30 min in vitro), mitigated protein tissue loss in mixed-parity sows, possibly due to reduced dietary AA oxidation and therefore a higher AA utilization for milk synthesis [16]. This was further confirmed in our recent study with 2 × 2 factorial design (8 vs 16 % slow protein in total protein × 140 vs 180 g/kg CP), in which we found that in multiparous sows, a higher slow protein concentration reduced postprandial plasma urea concentration and increased plasma AA availability, consequently leading to a greater milk production throughout lactation [17]. In addition, the reduction in body mobilization when feeding a high CP concentration was more pronounced when formulating diets for higher slow protein, possibly due to the improved dietary AA utilization [17].

In the current study, we investigated the effects of dietary AA availability on litter weight gain and body condition losses in primiparous sows, including body fat and protein tissue loss, and how the changes in body conditions affect conceptus survival and development and luteal functioning up to Day 8 post-ovulation. As a part of the 2 by 2 study [17], primiparous sows were allocated to one of two diets with the extreme contrast in AA availability: one with high CP (180 g/kg) and high in percentage of slow protein (16%) (HH), and one with low CP (140 g/kg) and low in slow protein (8%) (LL). We expected that the HH diet would reduce sow protein tissue loss, and improve indicators of metabolic status during lactation, such as plasma IGF-1 concentration. Moreover, we expected that sows that lost less body condition would have better conceptus development, luteal function and other reproductive parameters at Day 8 after ovulation.

2. Material and methods

2.1. Animals, housing and management

The current study was conducted along with a larger study with a 2 × 2 factorial design investigating effects of protein digestion kinetics (8 vs 16 % slow protein in total protein) and CP concentrations (140 vs 180 g/kg) on sow and litter characteristics during lactation [17]. Experiments were conducted at the Swine Research Facility of Trouw Nutrition R&D (Boxmeer, the Netherlands). The animal use protocols were reviewed and approved by the central committee for animal experiments in The Netherlands (approval number AVD20400202013805).

A total of 35 primiparous sows of a Yorkshire × Landrace genetic line (Hypor Libra, Hendrix Genetics, Boxmeer, the Netherlands) were used in this study. Sows were moved to the farrowing rooms 6.9 ± 0.2 days prior to farrowing. The temperature of the farrowing rooms was set at 22 °C around farrowing and decreased to 20 °C at weaning, and lights were on from 6:00 to 22:00.

After parturition (Day 0), piglets were treated according to the routine management practices on the farm, including tail docking within 24 h after birth, and no castration was performed. For sows that completed parturition after 16:30, the next day was considered as Day 0. Piglets with birth weight lower than 750 g were euthanized (total N = 14). Within 48 h post-farrowing, litters were standardised to 12–14 piglets, depending on the number of functional teats, and taking care litter size was similar across treatments. To maintain the litter size during lactation, any mortalities in litters were compensated by transferring piglets with birth weight >1000 g from reserve sows.

After 22.2 ± 0.2 days post-farrowing, sows were weaned and moved to the mating room. The temperature of the mating room was set at 20 °C, and lights were on from 06.00 to 22.00. From Day 1 post-weaning, oestrus detection was performed twice per day using a back pressure test, whilst a boar was placed in front of the sows. During standing heat, artificial insemination was performed once every 24 h.

2.2. Feeding and diets

Sows entered the farrowing crates at a body weight of 209.7 ± 2.4 kg, with estimated body protein of 32.7 ± 0.4 kg and estimated body fat reserves of 39.6 ± 0.9 kg, based on Dourmad et al. (1997) [18]. At that time, the sows were equally distributed over one of two lactation diets, that differed in AA availability by varying CP and slow protein concentration. The two dietary treatments were: low CP (140 g/kg) with a low percentage (8%) of slow protein in total protein (LL) or high CP (180 g/kg) with a high (16%) percentage of slow protein (HH). The difference in total dietary CP was achieved mostly by a change in soybean meal inclusion and synthetic amino acid inclusion while the change in percentage of slow protein to total protein was achieved mostly by replacing rapeseed meal by sunflower seed meal and wheat by maize. Diets were formulated as shown in Table 1. The percentage of fast, slow and resistant protein were defined as the nitrogen solubility reached at certain cut-off time points in an in vitro digestion model (fast: 0–30 min; slow: 30–240 min; resistant: after 240 min undigested protein), which were previously established for a range of ingredients based on [19]. The two diets were formulated to have equal concentration of net energy, ileal digestible essential AAs, and apparent total tract digestible phosphorus. The LL diet had a lower inclusion of non-essential AAs but a similar level of essential AAs to the high CP diet to meet the requirements. The HH diet was expected to lead to less body condition loss during lactation by sustaining a greater total AA availability in a more gradual way [15,16].

After entering the farrowing crates, sows received 2.7 kg/d of the allocated experimental lactation diet. On Day 1 post-farrowing, primiparous sows received 2.5 kg/d of one of the experimental lactation diets, and daily feed allowance was then increased stepwise to 7.0 kg/d on Day 21 post-farrowing. The feed curves were strictly followed to ensure equal intake across treatments. Sows were fed three times a day at 07.00, 12.00 and 16.00, with 30%, 30% and 40% of total daily feed allowance, respectively. Sows had unlimited access to water throughout the experimental period. The daily feed intake was calculated as feed allowance minus feed refusal, if any. From Day 1 post-weaning, sows were fed 3.1 kg/d of a standard gestation diet (CP = 140 g/kg, NE = 9.1 MJ/kg) until the day of scarification and dissection on Day 8 post-ovulation.

2.3. Body weight, BF and LM

Sow body weight and BF and LM thickness were measured on Day 1, Day 7, Day 14, and Day 21 post-farrowing before the morning feeding. The thickness of BF and LM were measured with a Brightness mode ultrasound device (MyLab™touchVet, Esaote S.p.A, Genoa, Italy) equipped with a 15 cm, 3.5 MHz linear probe. The probe was placed 50 mm lateral to the midline at the last rib and the BF and LM thicknesses were recorded at both sides of the midline. On the same days, the individual body weights of the piglets were recorded.

2.4. Collection of sow blood and faeces during lactation

On Day 14 post-farrowing, a 10 ml single blood sample was collected by jugular vein puncture, before and 4 h after the morning feeding,

Table 1
Ingredients and nutrient composition of experimental diets.

Ingredients, %	LL	HH
Wheat	34.470	35.932
Maize	14.39	23.23
Rye	23.9	3.8
Sunflower meal 38% CP	9.66	–
Soybean meal 46% CP	2.02	21.24
Soya hulls	–	7.90
Rapeseed meal, CP < 38%	–	–
Calcium Carbonate	1.53	1.4
Soybean oil	1.27	0.96
Wheat bran	5.1	–
Monocalcium phosphate	1.09	1.03
Potato protein, Ash <1.0%	–	–
Diamol DI 100K	1.0	1.0
Oats grain	3.6	–
Palm kernel flakes CF < 180	–	2.58
Na Bicarbonate	0.79	–
l-Lysine HCl 98%	0.524	0.101
Premix 1,25%	0.25	0.25
Salt (NaCl)	–	0.547
Wheat gluten meal	–	–
l-Threonine 98%	0.164	–
Iso Leucine	0.111	–
dl-Methionine 99%	0.034	0.015
Premixture	0.015	0.015
l-Valine 96.5%	0.058	–
L-Tryptophan 98%	0.024	–
Total	100	100
Composition (formulated)		
CP, g/kg	140	180
NE, MJ/kg	9.7	9.7
TDF, %	17.5	18.7
SID LYS, g/kg	8.1	8.3
SID M + C, g/kg	4.7	5.1
SID THR, g/kg	5.2	5.3
SID TRP, g/kg	1.6	1.9
SID VAL, g/kg	5.7	7.1
SID ILE, g/kg	4.4	6.3
SID LEU, g/kg	8.6	11.8
Slow Protein, % of total protein	8	16
Composition (Measured)		
CP, g/kg	136	177
GE, MJ/kg	15.5	15.9
ME, MJ/kg	13.3	13.4

LL = low CP (140 g/kg) and low percentage of slow protein (8%) diet, HH = high CP (180 g/kg) and high percentage of slow protein diet (16%), CP = crude protein, CF = crude fibre, NE = net energy, ME = metabolizable energy, SID = standardized ileal digestibility, LYS = lysine, M + C = Methionine + Cysteine, THR = Threonine, TRP = Tryptophan, VAL = Valine, ILE = Isoleucine, LEU = Leucine, TDF = total dietary fibre.

respectively. The samples were placed in an ice box for transportation to the laboratory and centrifuged at 3000×*g* for 15 min at 4 °C. After centrifugation, the plasma samples were stored at −20 °C prior to the assays of non-esterified fatty acid (NEFA), urea, creatinine and insulin-like growth factor-1 (IGF-1).

On Day 11.1 ± 0.3 post-farrowing, faeces samples were taken from the rectum for analysis of nitrogen, gross energy and acid-insoluble ash (AIA).

2.5. Post-weaning follicle development on day 3

From Day 3 post weaning, sows' pre-ovulatory follicle pools were detected transrectally twice a day at 12 h interval, with a Brightness mode ultrasound device (Aquila, Esaote S.p.A, Genoa, Italy), equipped with a 5-MHz curvilinear probe. On Day 3 post-weaning, the follicle size was defined as the mean diameter of the 5 largest follicles, with the diameter being the average of the longest diameter and the diameter that vertically intersected the middle point of the longest diameter of each follicle. Sows were considered to have ovulated once both ovaries were observed to have no pre-ovulatory follicles, and the time and date of ovulation was recorded.

2.6. Collection of sow blood, and reproductive organs after ovulation

On Day 8 post-ovulation, sows were sacrificed to harvest the reproductive organs. Firstly, sows were sedated by i.m. injection of Zoletil (Xylazine) and Sedamun (Tiletamine/Zolazepam). As sows were sedated, a 10 ml of blood sample was collected by jugular vein puncture. Filled tubes were placed in an ice box for transportation to the laboratory and centrifuged at 3000×*g* for 15 min at 4 °C. After centrifugation, plasma samples were equally split into 2 storage tubes, and then stored at −20 °C prior to the IGF-1 and P4 assays. Sows were then euthanized with injection of Euthasol.

After euthanization, the reproductive tracts (uterus and ovaries) were removed by midventral incision. Uterine horns were separated from the mesometrium and ovaries. The tubal end of both uterine horns were cut open to flush 30 ml DPBS through the uterine horns to flush out the conceptuses into a filter, taking care that the conceptuses remained suspended in fluid. The procedure was repeated and conceptuses with some of the flush medium were then transferred to petri dishes. The number of conceptuses from both uterine horns were counted. An eyepiece reticle fitted on the microscope was used to assess the longest conceptus diameter and the diameter perpendicular to it. These measures were averaged for conceptus size.

After collection of conceptuses, uteri were weighed and the uterine horns were straightened to measure the uterine length. The CL were counted and individually dissected and weighed to assess luteal weight.

2.7. Chemical analyses

The Dumas method [20] was used to determine the nitrogen (N) concentration of feed and faecal samples, and protein was calculated as N × 6.25. Gross energy levels of feed and faecal samples were analysed with an Automatic Isoperibol Oxygen Bomb Calorimeter. AIA was selected as the internal digestibility marker in this study and was spiked by adding diatomaceous earth to the diets. The recovery rate of AIA across different studies in pigs ranged from 0.91 to 1.00 as reviewed by Ref. [21]. The AIA concentration of feed and faecal samples was measured as described by Ref. [22].

Plasma samples were thawed before analyses. The NEFA, urea and creatinine concentrations in sow blood plasma were measured by using corresponding commercial colorimetric kits (NEFA, urea and creatinine: HUMAN, Wiesbaden, Germany) with an UV–Visible Spectrophotometers (Evolution™ 201, Thermo Scientific, Waltham, USA). The concentration of IGF-1 in sow plasma was detected by an enzyme-linked immunosorbent assay kit (Clould-Clone Corp., US).

2.8. Calculations

Protein and energy digestibility were calculated as follows:

Digestibility (%) = 100 – [(CIinput × CCoutput)/(CCinput × CIoutput) × 100], where CIinput and CIoutput were the concentration of AIA in feed and faeces, respectively; CCinput and CCoutput were the concentration of components in feed and faeces, respectively.

The metabolizable energy (ME, MJ/d) intake of a sow was calculated as follows: (gross energy of diets, MJ/kg * energy digestibility of corresponding diet, %) * (99.8–0.02 * CP, g/kg) * feed intake, kg/d [23].

To estimate sow body protein and fat mass, the equations of Dourmad et al. (1997) [18] were used, considering their estimations were based on a high number of sows and are still valid for current sows [24,25]. Body protein and fat mass were estimated as follows: Protein (kg) = 2.28 + (0.178 × 0.96 * SBW, kg) - (0.333*BF, mm) and Fat (kg) = −26.4 + (0.221 * 0.96 * SBW, kg) + (1.331*BF, mm), where SBW = Sow body weight, BF = Sow back fat.

Sow energy balance over the 21-day lactation (MJ ME) was calculated as follows: ((sow daily ME intake – 0.418 * ((SBW Day 1 post-

farrowing + SBW Day 21 post-farrowing)/2)$^{0.75}$ – (20.6 * average litter daily weight gain, g/d – 376 * litter size at weaning)/(1000*0.72))*21.

Sow plasma IGF-1 concentration on Day 14 post-farrowing was calculated as the mean concentration of pre-feeding and post-feeding plasma IGF-1 concentrations.

Litter gain during lactation as a proxy for milk production, was calculated as the sum of the individual piglet gains from birth to weaning. The piglet gains before and after cross-fostering were added separately to the corresponding litters. Weight gain for piglets with decreased body weight in a certain lactating period was corrected to 0 in the litter gain calculation. The body weight of piglets taken out of the experiment because of death or weakness was recorded to calculate the gain until removal.

Embryo survival (%) to Day 8 post-ovulation was calculated as: number of total conceptuses/number of CL.

2.9. Statistics

Effects of the dietary treatments on sow performance during lactation, including feed intake, body condition losses, blood metabolites, litter weight gain and subsequent reproductive parameters, and relationships between parameters, were analysed with SAS OnDemand for Academics (SAS Institute Inc., Cary, North Carolina, USA), using MIXED models and Pearson correlation tests. Normality of data and model residuals were checked using the UNIVARIATE procedure.

To test the effects of the diets on nutrient intake during a 21-day lactation of primiparous sows, and on their subsequent reproductive performance, the following MIXED model was used:

$$Y = \mu + \text{diets} + e \quad \text{(Model} \qquad 1)$$

Where Y = average daily feed intake (ADFI), ME intake or digestible protein intake during a 21-day lactation, follicle size on Day 3 post-weaning, weaning-to-ovulation interval (WOvI), plasma IGF-1 or P4 concentration, CL number and weight, conceptus number, survival, size and standard deviation (SD), or uterine weight and length on Day 8 post-ovulation, μ = overall mean, diets = LL/HH, e = residual error. Four sows (one HH sow and three LL sows) that had conceptuses larger than 1.5 mm most probably ovulated earlier than estimated, and were therefore excluded from all analyses related to ovulation time and slaughter findings, except for conceptus number and survival. Another two sows (one HH sow and one LL sow) were excluded from the analyses of number and survival rate of conceptuses as the filter was not installed properly during collection, resulting in a low recovery of conceptuses (12.5 ± 1.5).

Subsequently, ADFI and sow body condition measures on Day 1 post-farrowing (one by one: body weight, BF, LM, estimated body protein, estimated body fat) were added as covariates into Model 1, to analyse effects of initial sow body condition on sow body condition losses during lactation and on reproductive performance parameters.

ADFI was added as a covariate into Model 1 to analyse dietary effects on sow energy balance, and blood metabolites including urea, creatinine, NEFA and IGF-1 on Day 14 post farrowing. Litter size on Day 21 post-farrowing and ADFI were added as covariates to Model 1 to analyse dietary effects on litter weight gain during lactation and in different weeks of lactation.

For all models, interactions between explaining variables were excluded from the model if they were not significant.

To analyse the relations between sow plasma P4 and, IGF-1 concentration and sow reproductive parameters on Day 8 post-ovulation, the following MIXED model was used:

$$Y = \mu + X + e \quad \text{(Model} \qquad 2)$$

Where Y = sow plasma P4 or IGF-1 concentrations. X = plasma IGF-1 or P4 concentrations, CL number and weight, conceptus number, survival, size and standard deviation (SD), or uterine weight and length on Day 8 post-ovulation.

Pearson's correlation tests were also performed to test correlations between IGF-1 and P4 concentrations on Day 8 post-ovulation and sow subsequent reproductive performance.

In addition, body weight loss classes were defined (<9.85% (n = 11), 9.85–12.50% (n = 13) and >12.50% (n = 11)) and related to metabolic measures during lactation and reproductive performance, using:

$$Y = \mu + \textit{body weight loss class} + e \quad \text{(Model} \qquad 3)$$

Where Y = ADFI/Digestible protein intake/ME intake/Sow body weight on Day 1 and on Day 21 post-farrowing/Litter size on Day 21 post-farrowing/Litter gain Day 1 to Day 21/energy balance/Day 14 blood plasma metabolites/Follicle size Day 3 post-weaning/WOvI/sow reproductive parameters on Day 8 post-ovulation. The results are presented in Supplementary Table 1 and Supplementary Table 2.

3. Results

3.1. Effects of diets

During the 21-day lactation, the diets did not affect sow ADFI or ME intake, but the HH diet led to a higher digestible protein intake than the LL diet (Δ = 173 g/d, P < 0.01, Table 2). The diets had no impact on sow energy balance or body condition losses during lactation (Table 2). On Day 14 post-farrowing, sows fed the HH diet had significantly higher pre- and post-feeding plasma urea concentrations (Δ = 2.2 mmol/L, P < 0.01, Δ = 2.5 mmol/L, P < 0.01, respectively, Table 2) than sows fed the LL diet. No significant effects of diets on other blood metabolites were found on this day.

The diets did not affect litter weight gain when calculated over the 21-day lactation (Table 2). However, the litter weight gain of sows fed the HH diet tended to be higher than sows fed the LL diet in Week 3 (Δ = 1.3 kg, P = 0.09, Table 2), and combined for week 2 plus week 3 LL (Δ = 2.4 kg, P = 0.06, Table 2). No dietary effects were found on post-weaning reproductive performance (Table 2).

3.2. Effects of lactational body condition and body condition losses on reproductive parameters

Follicle size on Day 3 post-weaning was not affected by sow body condition loss during lactation, but positively related to both sow body weight and estimated body protein mass on Day 1 and Day 21 post-farrowing (all P < 0.01, Table 3). Estimated body fat mass on Day 1 post-farrowing was also positively related to follicle size (P = 0.04, Table 3).

On Day 8 post-ovulation, plasma IGF-1 concentration was positively related to BF thickness on Day 1 post-farrowing (P = 0.04, Table 3), and tended to be positively related to BF thickness on Day 21 post-farrowing (P = 0.09, Table 3). Plasma P4 concentration was negatively related to lactational loss of LM (P = 0.02, Table 3), BF (P = 0.02, Table 3) and estimated body fat (P = 0.01, Table 3). Conversely, P4 concentration was positively related to the energy balance during lactation (β = 0.04 ng/ml · ME MJ^{-1}, P < 0.01, Table 3).

CL number was negatively related to the BF thickness on Day 1 post-farrowing (P = 0.04, Table 3), but positively related to the energy balance during lactation (P = 0.02, Table 3). The weight of CL was positively related to the estimated body protein on Day 1 post-farrowing (P = 0.03, Table 3) and estimated body protein loss during lactation (P = 0.04, Table 3), and tended to be positively related to the body weight loss in kg (P = 0.09, Table 3). In contrast, the CL weight was negatively related to both the BF thickness on Day 1 (P = 0.02, Table 3) and Day 21 post-farrowing (P = 0.02, Table 3).

The total number of conceptuses on Day 8 post-farrowing tended to negatively related to BF thickness on Day 1 post-farrowing (P = 0.06, Table 3) and BF loss during lactation (P = 0.08, Table 3). The survival

Table 2
Effects of lactation diets on sow and litter characteristics during lactation and on subsequent sow reproduction characteristics (LS means ± SEM).

Item	Lactation diets			
	LL	HH	SEM	P-value
Day 1 to Day 21 post-farrowing,	N = 18	N = 17		
ADFI, kg/d	4.5	4.5	0.1	0.93
Digestible protein intake, g/d	533	707	15.0	<0.01
ME intake, MJ/d	60.6	60.0	1.5	0.88
Body weight loss, kg	23.5	24.2	2.2	0.77
Body weight loss, %	11.3	11.5	0.7	0.84
LM loss, mm	9.6	8.9	1.2	0.68
BF loss, mm	4.0	4.6	0.4	0.29
Estimated body protein loss, kg	2.7	2.6	0.2	0.80
Estimated body fat loss, kg	10.4	11.3	0.7	0.37
Energy balance, ME MJ	−819	−892	29	0.36
Day 14 sow blood plasma metabolites,	N = 18	N = 17		
pre-feeding urea, mmol/L	3.9	6.2	0.2	<0.01
post-feeding urea, mmol/L	4.2	6.6	0.2	<0.01
postprandial urea changes, mmol/L	0.2	0.5	0.2	0.46
pre-feeding creatinine, μmol/L	156.8	161.5	4.1	0.42
post-feeding creatinine, μmol/L	157.4	160.0	5.1	0.72
Postprandial creatinine changes, μmol/L	0.6	−1.6	3.9	0.70
pre-feeding NEFA, μmol/L	460.1	487.0	75.1	0.80
post-feeding NEFA, μmol/L	216.8	228.5	34.4	0.81
postprandial NEFA changes, μmol/L	−243.3	−258.5	80.2	0.89
Pre-feeding IGF-1, ng/ml	147.6	155.9	13.3	0.66
Post-feeding IGF-1, ng/ml	138.1	139.1	10.5	0.95
Postprandial IGF-1 changes, ng/ml	−9.5	−16.8	14.4	0.71
Litter size on Day 21 post-farrowing	13.0	12.9	0.1	0.31
Litter weight gain Day 1 to Day 21, kg	61.9	64.0	1.4	0.30
Litter weight gain Week 1, kg	19.8	19.4	0.6	0.67
Litter weight gain Week 2, kg	20.4	21.5	0.5	0.13
Litter weight gain Week 3, kg	21.7	23.0	0.5	0.09
Litter weight gain Week 2 + 3, kg	42.1	44.5	0.9	0.06
Day 3 post-weaning,	N = 18	N = 17		
Follicle size, mm	4.6	4.8	0.2	0.35
Ovulation,[x]	N = 17	N = 17		
WOvI, Days	6.3	5.7	0.3	0.17
Day 8 post-ovulation,	N = 16	N = 17		
Pregnancy rate	16/17	17/17		
IGF-1, ng/ml[y]	510.0	546.6	21.5	0.24
P4, ng/ml[y]	49.0	50.3	2.6	0.72
CL number[y]	23.5	22.2	0.9	0.31
CL weight, g[y]	10.8	10.3	0.6	0.53
Conceptus number[z]	21.5	21.2	1.0	0.82
Conceptus survival, %[z]	90.8	94.6	2.5	0.29
Conceptus size, mm[y]	0.81	0.83	0.04	0.74
Conceptus SD, mm[y]	0.13	0.15	0.01	0.17
Uterine weight, g[y]	798	846	34	0.33
Uterine length, cm[y]	279	297	15	0.41

LL = lactation diets with low CP (140 g/kg) and low percentage of slow protein (8%), HH = lactation diets with high CP (180 g/kg) and high percentage of slow protein (16%), ADFI = average daily feed intake, ME = metabolizable energy, LM = loin muscle, BF = backfat, NEFA = non-esterified fatty acid, IGF-1 = insulin like growth factor-1, WOvI = weaning-to-ovulation interval, P4 = Progesterone, SD = standard deviation, CL = corpus luteum.

[x] Excluding one sow that did not ovulate within 10 days after weaning.

[y] Excluding 4 sows in which ovulation was missed, as based on large conceptus size (>1.5 mm).

[z] Excluding 2 sows with partial conceptus collection.

rate of conceptuses tended to be positively related to LM thickness on Day 21 post-farrowing (P = 0.10, Table 3). With respect to the conceptus size on Day 8 post-ovulation, it was negatively related to the body weight loss both in kg (P = 0.01, Table 3, Fig. 1A), and in percentage (P < 0.01, Table 3, Fig. 1B). Equally, the conceptus size was negatively related to both the estimated body protein (P = 0.03, Table 3) and to the body fat losses during lactation (P = 0.04, Table 3). The energy balance during lactation was positively related to conceptus size on Day 8 post-ovulation (P = 0.01, Table 3, Fig. 1C). The SD of conceptuses on Day 8 post-ovulation was negatively related to BF loss (P = 0.05, Table 3), and tended to be negatively related to the estimated body fat loss during lactation (β = −0.01 mm/mm, P = 0.08, Table 3). Conversely, the SD tended to be positively related to the BF thickness on Day 21 (β = 0.01 mm/mm, P = 0.09, Table 3). Uterine weight and length were not related to sow body condition or energy balance during lactation.

Relationships between reproductive parameters, plasma IGF-1 and P4 concentrations on Day 8 post-ovulation.

Plasma P4 and IGF-1 concentrations were not correlated on Day 8 post-ovulation (Table 4). The P4 concentration was positively related with CL number (P_r = 0.02, P_β = 0.02, Table 4, Fig. 2A) and conceptus number (P_r = 0.01, P_β = 0.01,Table 4). Plasma IGF-1 concentration was negatively related to CL number (P_r < 0.01, P_β < 0.01, Table 4, Fig. 2B) and tended to be negatively related to the conceptus number (P_r = 0.06, P_β = 0.06, Table 4) and CL weight (P_r = 0.10, P_β = 0.07, Table 4). Conceptus survival rate, size and SD, and uterine weight and length were not related to either plasma P4 or IGF-1 concentration on Day 8 post-ovulation.

4. Discussion

In the present study, we examined the effects of dietary AA availability varied by dietary CP concentration and protein digestion kinetics, on sow litter weight gain and body condition losses, and studied relationships between sow body condition and metabolic status during lactation and subsequent reproductive performance parameters during early pregnancy. While the extent of body protein loss was not influenced by diets, increasing crude protein and slow protein concentrations tended to increase milk production. Maternal body condition loss during lactation, including body weight, body protein and body fat losses, negatively affected conceptus development at Day 8 post-ovulation. In addition to the lactational losses, also several sow body condition parameters at the start of lactation were related to reproductive measures in subsequent early pregnancy, including follicle size on Day 3 post-weaning, plasma IGF-1 concentration on Day 8 post-ovulation, and CL weight on Day 8 post-ovulation.

Based on a study with mixed parity sows [16], including protein sources with a slow digestion rate was expected to reduce body protein loss in lactating sows by reducing oxidation and improving utilization of dietary AA after absorption. In our recent larger study with a 2 by 2 factorial design (8 vs 16 % slow protein in total protein × 140 vs 180 g/kg CP), we found that at the same total CP concentration, sow postprandial plasma AA concentration and milk production were increased when formulating diets for a slower protein digestion rate [17]. Therefore, it was anticipated that increasing dietary CP as well as including protein sources with a slow digestion rate, would increase milk production and reduce loss of maternal protein pools in primiparous sows. Indeed, in the present study, diets tended to affect milk production, however, loss of body condition during lactation, and post-weaning measures of reproduction were not affected. The higher plasma urea concentration on Day 14 post-farrowing for the HH diet might indicate increased AA oxidation of surplus dietary non-essential AA.

Whereas sow reproductive performance was not affected by dietary treatments, we observed effects of sow body condition loss and energy balance on conceptus development at Day 8 post-ovulation, where higher body condition losses during lactation were associated with decreased average conceptus size. Sows that lost the highest amount of weight (>12.5% of post-farrowing weight) suffered from the most substantial negative energy balance during lactation, which was associated with a greater litter weight gain and lower lactation feed intake (Supplementary Table 1). On Day 8 post-ovulation, sows with lactation weight loss exceeding 12.5% had smaller conceptuses size (Supplementary Table 1). A smaller size of conceptuses can be related to lower conceptus protein and DNA content [26] and may indicate lower conceptus viability. A previous study demonstrated that more developed porcine conceptuses had a higher survival rate to Day 60 post-mating than less developed conceptuses when they were both transferred to recipients on day 6 of pregnancy, which indicated that more developed

Table 3
Estimates (β) of relationships between sow reproductive performance and sow body conditions on Day 1, Day 21 post-farrowing, sow body condition losses, and energy balance during lactation.

Item	Follicle size, mm[a]	WOvI, days	IGF-1, ng/ml[b]	P4, ng/ml[b]	CL number[b]	CL weight, g[b]	Conceptus number[b]	Conceptus survival, %[b]	Conceptus size, mm[b]	Conceptus SD, mm[b]
N	35	31	29	28	29	29	30	30	29	29
Body weight, kg										
Day 1 post-farrowing	**0.03***	$-1.0*10^{-3}$	−0.09	−0.13	−0.02	0.04	0.01	0.20	$1.3*10^{-3}$	$7.2*10^{-4}$
Day 21 post-farrowing	**0.04***	$-2.4*10^{-3}$	−0.55	−0.01	$7.9*10^{-4}$	0.01	0.04	0.19	$1.6*10^{-3}$	$4.9*10^{-4}$
Loss Day 1–21 in kg	0.02	$4.9*10^{-3}$	1.48	−0.39	−0.07	**0.10**$^{+}$	−0.06	0.06	**−0.01***	$1.1*10^{-3}$
Loss Day 1–21 in %	0.02	0.02	3.85	−0.83	−0.18	0.19	−0.22	−0.10	**−0.03***	$2.2*10^{-3}$
LM thickness, mm										
Day 1 post-farrowing	$-2.9*10^{-2}$	0.03	−1.99	−0.47	−0.01	−0.04	0.10	0.50	$2.1*10^{-3}$	$2.0*10^{-3}$
Day 21 post-farrowing	0.01	0.01	1.52	0.33	−0.05	−0.04	0.08	**0.54**$^{+}$	$2.1*10^{-3}$	$1.7*10^{-4}$
Loss Day 1–21	−0.01	0.01	−3.21	**−0.67***	0.03	$1.1*10^{-3}$	0.02	−0.02	$3.9*10^{-3}$	$2.1*10^{-3}$
BF thickness, mm										
Day 1 post-farrowing	0.01	0.02	**11.94***	**−1.27**$^{+}$	**−0.52***	**−0.38***	**−0.52**$^{+}$	0.14	$3.9*10^{-3}$	$7.4*10^{-4}$
Day 21 post-farrowing	0.01	0.08	**10.79**$^{+}$	−0.24	−0.29	**−0.43***	−0.21	0.27	$6.5*10^{-3}$	**0.01***
Loss Day 1–21	$1.1*10^{-3}$	−0.12	6.39	**−2.33***	−0.58	−0.06	**−0.67**$^{+}$	−0.16	−0.02	**−0.01***
Estimated body protein, kg										
Day 1 post-farrowing	**0.22***	−0.02	−6.22	−0.22	0.11	**0.43***	0.33	1.17	$7.3*10^{-3}$	0.01
Day 21 post-farrowing	**0.23***	−0.06	−8.99	−0.03	0.13	0.28	0.37	0.31	$8.7*10^{-3}$	0.01
Loss Day 1–21	0.17	0.13	5.02	−0.71	−0.01	**0.76***	0.14	0.60	**−0.06***	$8.5*10^{-4}$
Estimated body fat, kg										
Day 1 post-farrowing	**0.05***	−0.01	3.54	**−0.57**$^{+}$	−0.19	−0.07	−0.14	0.31	$3.0*10^{-3}$	$8.0*10^{-4}$
Day 21 post-farrowing	**0.05**$^{+}$	0.02	2.37	−0.10	−0.09	−0.11	−0.01	0.35	$4.2*10^{-3}$	$1.3*10^{-3}$
Loss Day 1–21	0.02	−0.04	3.92	**−1.32***	−0.30	0.08	−0.32	$-2.0*10^{-3}$	**−0.02***	**−0.01**$^{+}$
Energy balance, ME MJ	$-1.1*10^{-3}$	$6.1*10^{-4}$	−0.10	**0.03***	**0.01***	$7.9*10^{-4}$	0.01	−0.01	**$5.2*10^{-4}$***	$7.4*10^{-5}$

$^{+}$ Estimates with P-value < 0.1, * Estimates with P-value < 0.05.
[a] Day 3 post-weaning.
[b] Day 8 post-ovulation.
LM = loin muscle, BF = backfat, WOvI = weaning-to-ovulation interval, IGF-1 = insulin like growth factor-1, P4 = progesterone, SD = standard deviation, CL = corpus luteum, NEFA = non-esterified fatty acid, IGF-1 = insulin growth factor-1, BF = backfat.

conceptuses within the litter have advantage for survival to later gestating stage [27]. Hence, a smaller average conceptus diameter on Day 8 may result in higher embryonic loss at later stages, which could partly explain the reduced litter size often observed in sows with high body weight loss during the previous lactation [4,5,28], and the so-called 'second-litter-syndrome' observed in the second parity [29].

Follicular development along with oocyte maturation can be a critical factor determining embryo development, i.e. the size of conceptuses (reviewed in Ref. [30]). In the current study, with body weight loss varying between 5.5% and 19.1%, we did not find significant impacts of body condition loss on the size of the five largest follicles on Day 3 post-weaning, as established by ultrasound. However, in a previous study using primiparous sows, a higher body weight loss due to feed restriction during lactation was associated with a smaller size of the 15 largest follicles at dissection on Day 2 post-weaning [7]. Another study observed that sows subjected to a low level of feeding during lactation had higher lactational weight loss and reduced diameter of the 10 largest follicles at dissection on the day of weaning, but not on Day 2 post-weaning [31]. In a study by Ref. [32], sows at the first to second parity with higher LM loss during lactation had lower plasma IGF-1 concentration and smaller follicle size at weaning based on ultrasonic measurement, but not at Day 3 post-weaning or ovulation. The differences in the methods, range and time of measurements might be reasons for the lack of effects on the follicle size in the present study. In the study by Ref. [7], the smaller follicle size on Day 2 post-weaning in sows with high body weight loss was linked to less-expanded cumulus-oocyte complexes (COC) after in vitro maturation, and consequently, a lower percentage of zygotes reaching metaphase 24 h after in vitro fertilization. The later-maturing oocyte could be subsequently associated with less developed embryos on Day 4 post-mating, and those embryos remained less developed until Day 12 after being transferred to new recipients [8]. As folliculogenesis is a crucial phase for establishing DNA methylation of imprinted genes related to embryogenesis [33], a poor metabolic status during oocyte development may cause hypomethylation of maternally methylated imprinted genes within the oocytes, leading to subsequent embryonic growth retardation [34]. This was deemed a potential explanation for the less developed embryos on Day 30 of gestation found in second parity sows that had high lactational body weight loss during their first lactation [35]. Taken together, impaired follicle development and oocyte maturation due to poor metabolic status during lactation may affect embryonic growth, and such an effect is observable on Day 8 post-ovulation. Interestingly, although not affected by body condition losses, the follicle size on Day 3 post-weaning was increased by a higher body condition at farrowing and weaning. This might suggest that maintaining a proper body condition throughout the lactating period can be important to sustain proper subsequent follicle and embryo development.

In the present study, a higher pre-feeding plasma IGF-1

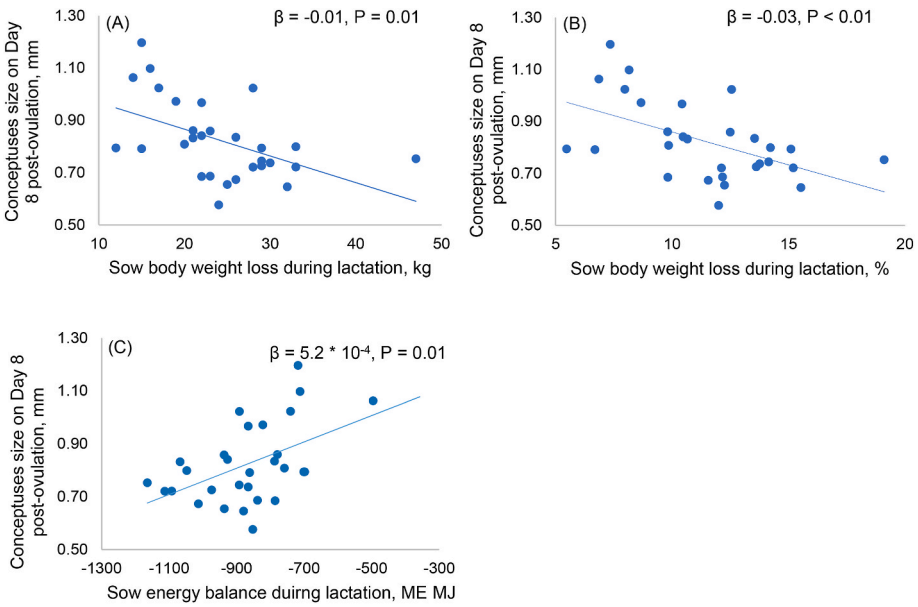

Fig. 1. Relationships between conceptus size on Day 8 post-ovulation (mm) and sow body weight loss (kg)(A), sow body weight loss (%)(B), and energy balance (ME MJ) during lactation.

Table 4
Relations between sow plasma progesterone (P4) and, Insulin-like growth factor-1 (IGF-1) concentration and sow reproductive parameters on Day 8 post-ovulation.

Item	P4, ng/ml		IGF-1, ng/ml	
	r	β	r	β
IGF-1, ng/ml	0.14	0.02	–	–
P4, ng/ml	–	–	0.14	1.32
Conceptus number	**0.53***	**1.18***	**−0.36**$^{+}$	**−7.88**$^{+}$
Conceptus survival rate, %	0.19	0.18	0.19	1.80
Conceptus size, mm	0.07	4.42	−0.19	−104.3
Conceptus SD, mm	−0.10	−16.82	0.09	139.9
CL number	**0.45***	**1.13***	**−0.51***	**−11.9***
CL weight, g	0.32	1.22	**−0.31**$^{+}$	**−10.93**$^{+}$

SD = standard deviation, CL = corpus luteum.
$^{+}$ Estimates with P-value < 0.1, * Estimates with P-value < 0.05.

concentration on Day 14 post-farrowing was found in sows that lost the least body weight (Supplementary Table 1). This was consistent with a previous study in which sows subjected to feed restriction lost more body weight and had lower plasma IGF-1 concentration on Day 17, 24 and 26 post-farrowing [7]. Moreover, sows that had a higher plasma IGF-1 concentration on the day before weaning maintained higher IGF-1 concentrations at weaning and on the day after weaning [31]. Based on these results, the plasma IGF-1 concentration might remain higher over the late lactation to post-weaning period in sows that lost less body condition in the current study. In another study, the higher plasma IGF-1 concentrations from mid-lactation to weaning resulted in a higher follicular IGF-1 concentrations on Day 2 post-weaning, and this was positively correlated with follicle size and subsequent COC expansion after in vitro maturation [7]. By binding to IGF-1 receptors on oocytes and granulosa cells, IGF-1 activates the phosphatidylinositol 3-kinase signalling pathway 1 by synergistically acting with FSH [36], consequently stimulating follicle growth, COC expansion, steroidogenesis and benefitting early embryo development [37–40]. Thus, the lower plasma IGF-1 concentration in sows with high weight loss might be one of the factors mediating negative effects on conceptus development in the present study.

The concentration of progesterone on Day 8 post-ovulation was negatively associated with loin muscle, backfat and estimated body fat losses, but increased with a higher energy balance during lactation. This is in agreement with a previous study that indicated that sows with a higher lactational weight loss under feed restriction had significantly lower progesterone concentrations on Day 4, 8, 12 and 16 post-mating compared to full-fed sows [10]. Similar detrimental effects of negative energy balance and lactational weight loss on progesterone concentration were also observed between 30 and 102 h post-ovulation [41,42]. Being the main progesterone secreting tissue during pregnancy, the total weight of CL had a positive relationship with systemic progesterone concentration on Day 5 of gestation [43]. In our study, the total CL weight increased with the total CL number (r = 0.45, P = 0.01, results not shown), and the latter was positively correlated with the plasma

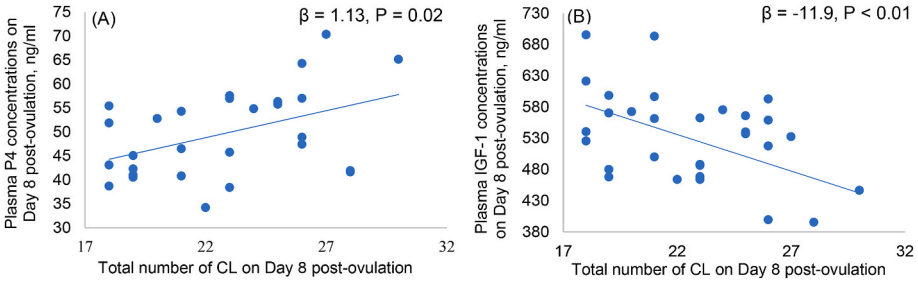

Fig. 2. Relationships between the total number of CL and plasma progesterone (P4) concentrations (A), and plasma Insulin-like Growth Factor-1 (IGF-1) concentrations (B) on Day 8 post-ovulation.

progesterone concentration on Day 8 post-ovulation. In addition, both the number of CL and progesterone concentration were higher but not significantly in sows with least body weight loss (Supplementary Table 1). Although it is not clear how metabolic status during lactation affects subsequent secretory function of CL, one explanation could be that the number and quality of follicle cells have further impacts on their secretory capacity after luteinisation, which is potentially mediated by IGF-1 and insulin [44]. Such a mediating role of IGF-1 might be supported by the current result that total CL weight on Day 8 post-ovulation was positively correlated with the post-feeding plasma IGF-1 concentration during lactation ($r = 0.32$, $P = 0.08$, Supplementary Table 2).

During early gestation, progesterone exerts crucial effects on conceptus survival and development [45]. Previous studies indicated that plasma progesterone concentration at 72 h was positively correlated with conceptus survival [46], but failed to establish an association between progesterone beyond 72 h with embryo survival (day 30 [46], day 35 [43]). In the current study, the progesterone concentration was not correlated with the conceptus survival at Day 8 post-ovulation, suggesting that such a positive relationship may only occur shortly after ovulation. Although plasma progesterone concentration was not directly related to the conceptus development on Day 8 post-ovulation, sows that had highest conceptus size had a numerically higher progesterone concentration (54.2 > 47.0 and 48.2 ng/ml, $P = 0.20$, Supplementary Table 1). Unlike the relative independency in the pre-hatching period, the conceptus development from Day 5 onwards can be modulated and supported by the uterine environment [11], where progesterone plays a modulating role in uterine protein synthesis and secretion [12]. It has been indicated that the rapidly increase in protein content in conceptuses during Day 8 to Day 9 of gestation may partly originate from the accumulation of uterine protein in the blastocoele, besides conceptuses own growth [11]. This might be in agreement with a previous study which found that uterine flushing associated with less-developed embryos on Day 12 had less total protein content [8]. In this case, the larger conceptuses observed in the current study may have benefitted from a more supportive uterine environment that was mediated by progesterone. However, these speculations need to be verified by future studies.

5. Conclusion

We found that the litter weight gain during week 2 to week 3 of primiparous sows tended to be increased when formulating diets for a high total crude protein and a slow protein digestion kinetics, whereas the body condition loss and reproductive parameters were not affected by the diets. A negative energy balance and sow body condition loss, including both body protein and fat loss during lactation, can impair subsequent conceptus development at Day 8 post-ovulation. Such retardation in conceptus growth can be attributable to defects in follicle development and oocyte maturation, which are likely mediated by IGF-1 during lactation. In addition, progesterone, as being influenced by weight loss and energy balance during the previous lactation, may be an important mediator to sustain conceptus development at early pregnancy stage by supporting the uterine environment. Besides the losses of body conditions during lactation, some reproductive parameters, such as follicle size, appear to be influenced by body condition at farrowing or weaning. Collectively, maintaining an optimal metabolic status and a proper body condition throughout the lactation is important for subsequent conceptus development and other associated reproductive parameters, which are crucial to the sow reproductive performance in the next parity.

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Declarations of competing interest

None.

CRediT authorship contribution statement

Hao Ye: Writing – original draft, Software, Investigation, Formal analysis, Conceptualization. **Nicoline M. Soede:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Bas Kemp:** Writing – review & editing, Supervision, Conceptualization. **Junjun Wang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Marleen Fleuren:** Software, Investigation, Data curation. **Bjorge Laurenssen:** Investigation, Data curation. **Emmy Bouwman:** Investigation, Data curation. **Pieter Langendijk:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors did not use any artificial intelligence-assisted technologies in the writing process.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.theriogenology.2024.02.003.

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